Functional Imaging in Mood Disorders

by

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ABSTRACT

Mood disorders are disabling psychiatric conditions which often present as lifelong illnesses. Many patients suffering from Major Depressive Disorder (MDD) experience only partial treatment success with pharmacotherapies, and patients suffering from Bipolar Disorder (BP) may continue to have difficulties maintaining a stable mood, despite medications. An increasing understanding of the neurobiology and neurocircuitry of the symptomatology of these disorders may advance treatment success or the development of new treatment strategies for patients. The current work was performed in light of advances in neuroimaging, specifically the emergence of functional magnetic resonance imaging (fMRI) which allows noninvasive measurement of brain activation. With the safety of fMRI less of a concern than older methods of brain imaging, we engaged in initial studies in healthy controls aimed at unraveling the brain activity changes associated with mania, in a dextroamphetamine-induced model for mania. Dextroamphetamine in healthy controls caused an overall decrease in brain activity in healthy controls, which may reflect the neurocircuitry changes in bipolar patients in a manic state, who are arguably more difficult to image directly. Two commonly prescribed mood stabilizers in the treatment of a manic episode are lithium and valproate. Healthy controls pretreated with either mood stabilizer, we found, compensated for the effects of dextroamphetamine, although in a task-dependent manner. In fact, lithium and valproate therapy alone also led to alterations in brain activity; decreases were observed in some tasks and not others.

Advancing our studies into the patient populations, we investigated brain activation changes in executive function in patients suffering from major depression and bipolar depression, compared to healthy controls. In both disorders, executive function has been reported to be impaired; since this is a high level cognitive process, a person's ability to perform at work and in their every day life may be influenced. The results of this investigation have demonstrated that patients suffering from major depression engage the right prefrontal cortex more than healthy controls and more than bipolar depressed patients. These results demonstrate that there are significant differences in brain activity between the two disorders, even though they may resemble each other in aspects of symptom presentation.

We believe that the current studies have substantial impact and have contributed greatly to our current knowledge of brain function in the mood disorders.

DEDICATION

For my family, and especially my parents, who have instilled in me the idea that one can effect change in the world. As I embark on new journeys in my career and life, I thank them for their unwavering support and their guidance.

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LIST OF ABBREVIATIONS

AAL	Automatic anatomic labeling
ACC	Anterior cingulate cortex
AC-PC	Anterior commissure- posterior commissure
ADHD	Attention deficit hyperactivity disorder
AFNI	Analyis of functional NeuroImages
ANOVA	Analysis of variance
APA	American Psychiatric Association
BDNF	Brain derived neurotrophic factor
BOLD	Blood oxygen level dependent
BP	Bipolar Disorder
BP I	Bipolar type I Disorder
BP II	Bipolar type II Disorder
BPD	Bipolar depressed
BD/d	Bipolar Disorder, depressed
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	Cerebral blood flow
CGM	Cerebral glucose metabolism
CMRglu	Cerebral metabolic rate of glucose
COWAT	Controlled oral word association test
CUN	Cuneus
DBP	Diastolic blood pressure
DLPFC	Dorsolateral prefrontal cortex

DSM-IV	Diagnostic and Statistical Manual for Mental Disorders, 4th Edition
EEG	Electroencephalogram
fMRI	functional magnetic resonance imaging
FWHM	Full width half maximum
GLM	General linear model
HC	Healthy control
HZ	Hertz
HAM-D	Hamilton depression rating scale
ID/ED	Intradimensional / extradimentional set shifting test
LDLPFC	Left dorsolateral prefrontal cortex
LINS	Left insula
LIOG	Left inferior occipital gyrus
LIP	Left inferior parietal gyrus
LLG	Left lingual gyrus
LMF	Left middle frontal gyrus
LMOG	Left middle occipital gyrus
LPCG	Left precentral gyrus
lPFC	lateral prefrontal cortex
LSF	Left superior frontal gyrus
LSP	Left superior parietal gyrus
LST	Left superior temporal gyrus
LVLPFC	Left ventrolateral prefrontal cortex
MADRS	Montgomery-Asberg Depression Rating Scale

MAOI	Monoamine oxidase inhibitor
MDD	Major Depressive Disorder
MDE	Major depressive episode
mg	milligram
MNI	Montreal Neurologic Institute
mPFC	medial prefrontal cortex
MR	Magnetic resonance
MRI	Magnetic resonance rmaging
MRS	Magnetic resonance spectroscopy
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
PI	Phosphoinositol
RDLPFC	Right dorsolateral prefrontal cortex
RINS	Right insula
RIOG	Right inferior occipital gyrus
RIP	Right inferior parietal gyrus
ROI	Region of interest
RLG	Right lingual gyrus
RMF	Right middle frontal gyrus
RMOG	Right middle occipital gyrus
RPCG	Right precentral gyrus
RPMT	Ravens progressive matrices task
RT	Reaction time

RSF	Right superior frontal gyrus
RSP	Right superior parietal gyrus
RST	Right superior temporal gyrus
RVLPFC	Right ventrolateral prefrontal cortex
SBP	Systolic blood pressure
SCID	Structured clinical interview for DSM-IV
SD	Standard deviation
SEM	Standard error of the mean
SMA	Supplementary motor area
SNRI	Selective serotonin noradrenaline reuptake inhibitor
SPECT	Single photon emission computed tomography
SPM	Statistical parametric mapping
SSRI	Selective serotonin reuptake inhibitor
SVC	Small volume correction
TCA	Tricyclic antidepressant
TE	Echo time
THA	Thalamus
TMT-B	Trail making test- part B
TOL	Tower of London
TR	Repetition time
VAS	Visual analogue scale
VLPFC	Ventrolateral prefrontal cortex
WAIS	Weschler adult intelligence scale

WCST	Wisconsin card sorting test
YMRS	Young mania rating scale

Chapter 1. Introduction

1.1 Mood Disorders

Affective disorders are characterized by changes in mood beyond what would be considered a *normal* response (Stahl, 2006). The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classifies mood or affective disorders according to two categories, unipolar major depressive disorder (MDD) and bipolar disorder (BP) (American Psychiatric Association (APA), 1994). The spectrum of mood is contained between two extremities, mania (hyper-elevated mood) and depression (decreased mood). Patients suffering from MDD experience periods of significantly depressed mood only, while patients with BP spend periods of time both in a depressed state and in a hyper-elevated mood state (mania or less severe hypomania) (Stahl et al., 2006).

1.1.1 Unipolar Depression (MDD)

Diagnosis

A diagnosis of MDD is made by fulfillment of a number of criteria laid out in the DSM-IV, which represent the occurrence of a cluster of symptoms (Stahl et al., 2006). For diagnosis of a major depressive episode (MDE), patients must display a significantly depressed mood or anhedonia (loss of interest or pleasure in things normally enjoyed) which persist for over 2 weeks. They must also display or report at least four additional symptoms which include weight changes, sleep difficulties, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, difficulties in concentration and recurrent thoughts of death, during this 2 week period (APA, 1994). Experiencing two or more MDEs separated by periods of wellness of at least two months results in the diagnosis of MDD (Parikh et al., 2001). The incidence of MDD is approximately 5% in the population and the recurrence risk is great, such that a patient who has suffered three depressed episodes has a 90% chance of subsequent recurrence (Stahl 2006). Patients suffering from MDD have an average age of onset from their early 20's to early 30's, and commonly patients who present for the first time have a history of previous depressed episodes (Stahl, 2006; Parikh et al., 2001). Additional factors play a role in impacting one's risk for MDD, including gender and family history (Stahl, 2006; Nierenberg, 2001). It is common for patients to suffer from comorbid disorders such as anxiety disorders and substance abuse/dependence, as well as chronic medical illness such as migraine, cancer or myocardial infarction (Parikh et al., 2001).

Treatment

Untreated, most episodes of depression last approximately 6-24 months (Stahl, 2006). In patients treated with an antidepressant the goal is to achieve a complete remission of symptoms. However, more often the efficacy end point in clinical trials is the observation of a significant response (reduction in depression) (Stahl, 2006). Current antidepressant treatment is only moderately effective, and only two-thirds of depressed patients respond to antidepressants (Stahl 2006) or achieve remission (Trivedi et al., 2006). In addition, some patients who respond will relapse (Nierenberg, 2001; Kennedy et al., 2001). Patients who have suffered previous episodes, more severe episodes, incomplete recovery between multiple episodes or psychotic features are at a greater risk for relapse (Stahl, 2006), and patients who have longer or more hospital stays, poorer family functioning and comorbid illness also have decreased chance for recovery (Parikh et al., 2001).

Current treatments for depression include several groups of antidepressant pharmacotherapies, namely the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), the selective serotonin reuptake inhibitors (SSRIs) and the novel agents.

Monoamine Oxidase Inhibitors (MAOIs)

The MAOIs were the first pharmacotherapies shown to be effective for the treatment of depression. The immediate mechanism of action of these drugs is to inhibit the enzyme MAO which functions to metabolize monoaminergic neurotransmitters including noradrenaline and serotonin (Stahl, 2006). However, because of a high risk for hypertensive crisis when administered in combination with foods containing high tyramine levels or other sympathomimetic substances, these drugs are generally not recommended as first line therapies for the treatment of depression (Stahl, 2006; Kennedy et al., 2003; Sadock and Sadock, 2003). However, these drugs may still be favored in treatment-refractory cases of MDD (Kennedy et al., 2001).

Tricyclic Antidepressants (TCAs)

TCAs, including the drugs amitriptyline and imipramine, were discovered to have antidepressant properties by the 1960s. Most TCAs block the reuptake of serotonin and noradrenaline into the presynaptic neuron, although they differ in the degree to which they block each of these (Stahl, 2006). TCAs can be considered as a second line therapy for major depression, although they may be more efficacious than SSRIs in inpatients and may be favored in treatment of refractory patients (Kennedy et al., 2003; Kennedy et al., 2001). The side effect profile of these antidepressants can be significant, including weight gain, drowsiness, blurred vision, dry mouth, dizziness and hypotension (Nierenberg, 2001). In addition, these drugs carry a potential for cardiac arrest or seizures in overdose (Stahl, 2006).

Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs (i.e. fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram) are a first line therapy for the treatment of MDD (Kennedy et al., 2003, Kennedy et al., 2001). The SSRIs are more powerful serotonin reuptake inhibitors than TCAs and they act distinctly, leaving noradrenaline reuptake transporter function relatively intact. In addition, the SSRIs have a reduced interaction with other receptors (histamine, acetylcholine, adrenergic receptors), presenting, in general, a less worrying side effect profile (Stahl, 2006). The SSRIs also carry a reduced risk of overdose compared to the TCAs (Sadock and Sadock, 2003).

Novel Agents

Novel agents, such as bupropion, venlafaxine and mirtazapine have differing mechanisms of action in the brain. Bupropion acts as a dopamine reuptake blocker, and has additional effects as a noradrenergic reuptake blocker, causing increased turnover of noradrenaline

(Feighner, 1999). Venlafaxine's selective blocking of the reuptake of serotonin and (at higher levels of the drug) noradrenaline, have resulted in this drug being named a serotonin-noradrenaline reuptake inhibitor (SNRI). Unlike the TCAs, venlafaxine does not interact significantly with other receptors (Feighner, 1999). Alternatively, mirtazapine's mechanism of action, while still causing an increase in serotonergic and noradrenergic activity, occurs because of its ability to block specific serotonin and noradrenergic receptor subtypes (Feighner, 1999). These novel agents may also be considered as first line therapy for MDD (Kennedy et al., 2003, Kennedy et al., 2001). It has been suggested that venlafaxine therapy, in particular, has shown some evidence of a greater remission or response rate in patients, over SSRIs (Stahl, 2006; Kennedy et al., 2003, Kennedy et al., 2001; Nierenberg, 2001).

Biological Basis of Depression

Theories of the biological basis of depression have generally evolved through the discovery of mechanisms of action of antidepressants in the brain. Early on, the pathophysiology of depression was thought to be explained by a functional deficiency in monamine neurotransmitters, which could effectively be reversed by antidepressants, causing the accumulation of these neurotransmitters in the synapse (TCAs, SSRIs) or preventing their breakdown (MAOIs) (Stahl, 2006). Also in support of this theory was the appearance of depression after the administration of drugs that decreased these neurotransmitters (Stahl, 2006). The monoamine hypothesis of depression, however, has proved to be an overly simplistic model of the biological changes occurring in MDD.

Biological dysregulations in neurotransmitter receptor expression are also observed in depression. The neurotransmitter receptor hypothesis of depression suggests that it is an upregulation of postsynaptic neurotransmitter receptors, which occurs because of a decreased amount of available neurotransmitter, that in turn results in depression (Stahl, 2006). Unfortunately, there is limited data to support the presence of an irregular expression of neurotransmitter receptors in depression.

Most recent biological theories of depression revolve around alterations in gene expression and in particular decreased expression of neurotrophic factors, such as brain derived neurotrophic factor (BDNF), which govern the viability of neurons (Castren et al., 2007; Stahl, 2006). Theoretically, a decrease in the expression of neurotrophic factors, occurring because of chronic stress in a depressed patient, would lead to detrimental changes in the brain, including cell death in the vulnearable hippocampus. There is ample evidence to suggest that chronic stress results in changes in neurostransmitter levels, decreased neurogenesis and increased cell atrophy and impaired cognitive abilities (Russo-Neustadt and Chen, 2005). In the presence of chronic stress, it has been suggested that hippocampal cells decrease expression of BDNF, and under the influence of increased levels of glucocorticoids undergo cell atrophy (Russo-Neustadt and Chen, 2005). In fact, some studies have shown decreased brain volume in patients with MDD (Castren et al., 2007; see Sheline 2003 for a full review). Addtionally, there is evidence suggesting that antidepressants may have a significant role in promoting cell survival through neurotrophic factors. Studies have demonstrated that antidepressants effectively increase the expression of genes for neurotrophic factors (Castren et al., 2007), and increase BDNF in the hippocampus (Russo-Neustadt and Chen, 2005), as well as block the decrease in BDNF, which occurs in response to chronic stress (Young et al., 2002).

The specific pathophysiology of MDD today is still unclear. However there are likely many biological factors which impact the patients risk for developing the disorder, the expression of the disorder, and a patient's response to treatment.

1.1.2 Bipolar Disorder (BP)

Diagnosis

It is common to distinguish between bipolar I disorder (BP I) and bipolar II disorder (BP II) when making a diagnosis in a patient with bipolar disorder. These subdivisions of the illness refer to different patterns of expression of the disorder. Patients suffering from BPI experience at least one episode of mania and usually periods of depression (MDEs). This is contrasted with patients who suffer from BPII who experience hypomanic episodes as well as major depressive episodes (MDEs) (Mitchell et al., 2004). Therefore the key difference between the two is the appearance of mania in BP type I opposed to hypomania in BP type II. The diagnosis of a manic episode, as described in DSM-IV, involves at least a one week period (or hospitalization) where mood is abnormally elevated and expansive (or irritable) and includes three of the following symptoms; inflated self-esteem, decreased need for sleep, increased talking, flight of ideas, distractibility, increased goal directed activity, excessive involvement in activities with high potential for painful consequences (Stahl, 2006). The diagnosis of a hypomanic episode is made for a shorter period of hyper elevated mood, lasting 4-7 days, in the absence of marked impairment. The age of onset of BP is generally earlier than that of MDD, episodes beginning between the teens and thirties (Benazzi, 2007; Thase, 2005). The prevalence rate of bipolar disorder is approximately 1%, although taking into account a broad definition of BP II, the prevalence rate may be as high as 6-11% (Thase, 2005; Mitchell et al., 2004). Partly, this variance in the reported prevalence may be explained by misdiagnosis of the disorder. Patients with BP spend the majority of their time in the depressed phase of the condition (Mitchell et al., 2004). In BP II patients, this is especially true, as they may spend as much as 50% of the time in a depressed state, which makes them prone to a misdiagnosis of unipolar MDD (Thase, 2005; Mitchell et al., 2004). There is a high risk of comorbidity in these patients, including anxiety disorders and substance use disorders (Mitchell et al., 2004).

There is some question as to the validity of BP I and BP II representing distinctly different forms of this illness (Mitchell et al., 2004). Potentially these represent different severities of the disorder and should be considered along a "bipolar spectrum" (Silverstone and Silverstone, 2004). Additionally, there has also been suggestion of a continuity between BP II and MDD, although other clinical factors may differentiate between the two disorders (Benazzi, 2007; Berk and Dodd, 2005).

Treatment

It has been reported that BP patients experience a high rate of disability, disrupted relationships, and higher unemployment rate than the general population (Mitchell et al., 2004). Additionally, there is a significant risk of suicide in bipolar patients when depressed (Lopez et al, 2001; Muller-Oerlinghausen et al, 2002), with as many as 34% of patients attempting suicide (Leverich et al, 2003). Appropriate diagnosis and effective treatment in BP in the manic, depressed and asymptomatic phase should be a key goal in the management of BP (Silverstone and Silverstone, 2004). However, as most randomized controlled trials have been conducted in BP I, the most effective management of BP II is still somewhat unclear (Mitchell et al., 2004).

Acute treatment of bipolar mania

Lithium, the original mood stabilizer drug, remains an effective first line therapy in acute mania (Yatham et al., 2007; Mitchell et al., 2004). There is also a well established literature to support the use of the anticonvulsant drug valproate in the management of an acute manic episode (Yatham et al., 2007; Mitchell et al., 2004). Additionally, randomized controlled trials have shown efficacy in the treatment of acute mania with the atypical antipsychotics olanzapine, risperidone and quetiapine. Finally, first line therapy may also include the combination of either lithium or valproate with an atypical antipsychotic (Yatham et al., 2007).

Acute treatment of bipolar depression

The treatment of bipolar depression has in the past been dominated by antidepressant therapies (Mitchell et al., 2004). However, antidepressant therapy in BP carries a risk of manic switch or the induction of rapid cycling (Mitchell et al., 2004). Today, the most recent first line treatment recommendations in Canada for bipolar I depression include the use of lithium or the anticonvulsant lamotrigine, which also may prevent the recurrence of bipolar depression (Yatham et al., 2007; Mitchell et al., 2004). Monotherapy with the atypical antipsychotic quetiapine has recently been added as a first line therapy in bipolar depression (Yatham et al., 2007). Combination therapies, including the addition of an antidepressant to lithium or valproate are also suggested first line options (Yatham et al., 2007). However, venlafaxine is not recommended in bipolar depression as it may present a higher risk of manic switch than bupropion or sertraline (Yatham et al., 2007; Post et al., 2006). To date, there remains insufficient evidence from randomized controlled trials to support a recommended effective first line therapy in acute bipolar II depression, although first line maintenance therapy in this population is suggested to include monotherapy with lithium or lamotrigine (Yatham et al., 2007).

Maintenance therapy of bipolar disorder

There may be some benefit in psychosocial interventions in the maintenance of bipolar patients. However, lithium, lamotrigine, valproate and olanzapine have all shown first line evidence to support a prevention of manic and depressed episodes when used as maintenance therapy for bipolar disorder (Yatham et al., 2007). When these are unsuccessful, a variety of combination therapies, including mood stabilizers (lithium, valproate, lamotrigine), atypical antipsychotics (olanzapine, quetiapine, rispiridone) and antidepressants (buproprion, SSRIs) may be used as second line therapy (see Yatham et al., 2007 for a full review).

Biological Basis of Bipolar Disorder

The underlying basis of BP remains uncertain despite many hypotheses. Because the functional neuroimaging data will be reviewed elsewhere in this thesis, and because the pathophysiological findings in BP are not conclusive, only a brief explanation of some current areas in BP pathology investigation are mentioned here.

Twin studies and investigations in probands reveals that there is a strong genetic contribution in BP; first degree relatives are at 13 times increased risk of developing the disorder (Mitchell et al., 2004). However, there are likely a variety of environmental factors that also increase vulnerability to the illness (Post et al., 2003). Specific genetic markers for BP have not yet been identified.

In the last 10 years, there has also been a renewed interest in the clinical mechanism of action of mood stabilizer medications. Lithium, which originally was thought to exert its effects through modulation of second messenger systems, has been found to have properties as a neuroprotective and neurotrophic agent (Post et al., 2003, Young et al., 2002). In animals, lithium increases neurogenesis, and cell survival after cerebral insults. Additionally, lithium increases the levels of the antipoptotic factor Bcl-2 and the neurotrophic factor BDNF in vitro. The neurotrophic actions of lithium may play an important role in its clinical efficacy, and this idea is supported by the fact that valproate, a different class of drug but also a mood stabilizer, also increases Bcl-2 (Post et al., 2003).

1.2 Functional Neuroimaging in Mood Disorders

Over the last 15 years there has been a great increase in the number of functional imaging studies in mood disorders, following the advent of functional magnetic resonance imaging (fMRI). Unfortunately, these studies have largely proven difficult to compare and contrast because of differences in patient groups, symptomatology and treatment effects. Additionally, many studies have used small sample sizes and have investigated different hypotheses, which make comparisons even more difficult to make. The following section reviews some of the current findings from neuroimaging research of functional brain changes in depression and in BP.

1.2.1 Functional Neuroimaging in Major Depressive Disorder

The limbic-cortical model of depression, proposed by Mayberg (1997; 1999) suggests that depressive symptoms can be accounted for by dysregulations in dorsal (dorsolateral prefrontal cortex), ventral (ventral prefrontal cortex, anterior cingulate, amygdala and insula) and rostral (anterior cingulate) regions of the brain, which intercommunicate. In this model, the dorsal regions modulate the impairments in executive function and cognition that are observed in major depression, while the ventral components influence appetite and sleeping problems as well as emotional regulation difficulties. The rostral component is suggested to serve a modulatory role in the communication between the dorsal and ventral regions (Deckersbach et al., 2006). This section of the thesis will briefly review the functional neuroimaging data which has contributed to the development of this model.

Resting brain: Positron emission tomography (PET) and single photon emission computed tomography (SPECT) in depression

Studies of regional cerebral blood flow (CBF) and regional cerebral glucose metabolism have consistently demonstrated decreases in CBF in unipolar depression, particularly in the frontal lobe (Mayberg et al., 1994; George et al., 1994; Baxter et al., 1989). Specific decreases in regional CBF and metabolism have been observed in the dorsolateral prefrontal cortex (DLPFC), and dorsal anterior cingulate, while increases in CBF and metabolism have been observed in orbitofrontal cortex, amygdala and insula as well as in the rostral anterior cingulate (see Deckersbach et al., 2006 for a review).

Mood challenges: Functional brain changes due to sadness

In healthy controls, the induction of sadness results in increased CBF in the ventral prefrontal cortex and insula, coupled with a decreased CBF in the DLPFC (Drevets, 2001; Damasio et al., 2000; Mayberg et al., 1999). Before treatment, depressed patients demonstrate decreased activity in the DLPFC and increased activity of the ventral prefrontal cortex, insula, amygdala and hippocampus (Deckersbach et al., 2006). The agreement between the mood induction data in healthy controls and the data obtained in depressed patients substantiates the involvement of these brain regions in the pathophysiology of the illness, and Mayberg's model of dorsal hypoactivity and ventral hyperactivity in depression. Moreover, after treatment, it has been observed that the functional dysregulations in depression, which look like sadness in healthy controls, are normalized (Mayberg et al., 1999).

Cognitive activation: Functional brain changes during cognitive challenges

Studying brain activity and CBF in patients during the completion of specific cognitive tasks may help delineate additional abnormalities in brain function that impact the affective and cognitive components of major depression. In depressed patients, cognitive task performance has demonstrated dysregulations of the DLPFC and the anterior cingulate (Deckersbach et al., 2006), and these changes in activity have been suggested as the basis for memory and attentional difficulties in patients. Additionally, challenging subjects with a cognitive task containing a negative affective component has shown that depressed patients have increased activation of the amygdala, compared to healthy subjects, which does not release when the negative affective component is removed (Siegle et al., 2002; Semple et al., 1993).

Over the last few years years, the suggestion of distinct neural models of depression have been crucial in the development of new treatment options (deep brain stimulation) (Mayberg et al., 2005) and in developing new ways to gauge treatment success. Functional imaging data have been an integral component in corroborating a dorsal hypoactivity and ventral hyperactivity in depression.

1.2.2. Functional Neuroimaging in Bipolar Disorder

Unfortunately, there is a less succinct understanding of the contribution of functional brain changes to the pathophysiology and symptomatology of BP. The difficulties of performing studies when patients are in numerous phases of the illness, have different subtypes of the illness, are on different medications, and have different courses of illness means that there is a limited agreement across neuroimaging studies to date. However, this section provides an overview of the functional neuroimaging data in BP patients. Additionally, this section includes any comparisons of functional-metabolic activity which have been made between BP patients and MDD patients

Cerebral Blood Flow

Studies examining cerebral blood flow (CBF) do not suggest differences between BP I patients and BP II patients, although these have never been compared directly (McGrath et al., 2004). However, there are differences in CBF observed between symptom states in manic/hypomanic BP patients. Two studies have reported increased CBF in the temporal (Gyulai et al. 1997) and limbic (Blumberg et al. 2000; Rubinsztein et al. 2001) regions. A third study found reduced CBF in the frontal lobe (Blumberg et al. 1999; Rubin et al. 1995; O'Connell et al. 1995; Rubinsztein et al. 2001) relative to HC. Among manic BP I patients, reduced CBF has also been reported in the temporal lobes (Migliorelli et al. 1993), and increased CBF has been reported in the basal ganglia (O'Connell et al. 1995).

Increased temporal lobe CBF has also been reported in depressed BP patients relative to euthymic BP patients (Gyulai et al. 1997). In euthymic BP I patients, following lithium discontinuation, CBF has been reported to increase in the temporal and decrease in the limbic regions (Goodwin et al. 1997). In studies examining depressed BP II patients, CBF is reduced in temporal, frontal and limbic regions in most (Ito et al. 1996; Bonne et al. 1996), but not all (Tutus et al. 1998), studies when compared to HC.

There are only a few studies that actually compare BP patients to MDD patients. Of those studies which have examined both groups, three found decreases in temporal, limbic, and frontal regions in both BP and MDD patients (Ito et al., 1996; Bonne et al., 1996; Marangell et al., 1997), while another found that BP patients had lower frontal lobe CBF than MDD patients (Tutus et al., 1998). See Table 1.1 for a review of CBF findings in bipolar patients.

Table 1.1: Cerebral blood flow (CBF) in bipolar disorder- literature review.

Summary of the data from single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroimaging studies to date, illustrating where there are increases (⇑), decreases (⇓), or no changes (⇔) in cerebral blood flow (CBF) between specific therapeutic groups and healthy controls (HC). The table also indicates the number of patients (N) included in each study.

Cerebral Blood Flow (CBF)

Study	N	Findings	Notes
Migliorelli et al. 1993	5	- ↓right basal temporal lobe CBF in manic BP-I patients compared to HC. - ↓perfusion in right vs. left (left-right asymmetry) basal temporal lobe in manic BP-I patients compared to HC. - ↓perfusion in vs. dorsal (ventral-dorsal asymmetry) right basal temporal lobe in manic BP-I patients compared to HC.	All Female Drug Free
O'Connell et al. 1995	11	- ↓prefrontal cortex CBF in manic BP-I patients and patients with schizophrenia compared to HC. - ↓prefrontal cortex CBF in patients with schizophrenia compared to manic BP-I patients. - ↑basal ganglia CBF in manic BP-I patients compared to HC.	Various medications
Rubin et al. 1995	11	- ↔global CBF between manic BP-I patients, MDD patients and HC. - ↓frontal and anterior cortical CBF in manic BP-I patients and MDD patients compared to HC.	Drug Free
Ito et al. 1996	6	- ↓anterior superior and middle frontal gyri, right anterior cingulate cortex, left anterior superior temporal gyrus, and anterior insular cortex CBF in depressed BP-II patients and MDD patients compared to HC. - ↔left angular gyrus, and left lingual gyrus CBF between depressed BP-II patients and to HC.	Various medications
Bonne et al. 1996	20	- ↓superior temporal, right parietal and bilateral occipital CBF in depressed BP-II patients and MDD patients compared to HC.	Drug Free
Goodwin et al. 1997	14	- ↑left middle inferior posterior temporal cortex (posterior) CBF following lithium discontinuation in euthymic BP-I patients, independent of manic onset. - ↓left anterior cingulate gyrus (anterior) CBF following lithium discontinuation in euthymic BP-I patients, independent of manic onset.	Lithium withdrawal
Gyulai et al. 1997	12	- ↑left anterior temporal lobe CBF in depressed BP (I and II) patients compared to euthymic BP (I and II) patients, irrespective of plasma lithium level. - ↑right anterior temporal lobe CBF in hypomanic/manic BP (I and II) patients compared to euthymic BP (I and II) patients.	Lithium Rapid cycling
Marangell et al. 1997	39	- Serum thyrotropin-stimulating hormone (TSH) inversely correlated with both global CBF in patients with BP (I and II) and MDD. - TSH inversely correlated with left DLPFC and mesial prefrontal CBF in patients with BP (I	Drug Free

Marangell et al. 1997	39	- Serum thyrotropin-stimulating hormone (TSH) inversely correlated with both global CBF in patients with BP (I and II) and MDD. - TSH inversely correlated with left DLPFC and mesial prefrontal CBF in patients with BP (I and II) and MDD. - ↔ CBF between BP (I and II) patients and MDD patients, irrespective of gender.	Drug Free
Tutus et al. 1998	7	- ↓ left frontal CBF in depressed BP-II patients and HC compared to MDD patients. - ↔ frontal, parietal, temporal and occipital CBF between depressed BP-II patients and HC.	Drug Free
Blumberg et al. 1999	11	- ↓ right middle frontal gyrus and orbitofrontal cortex CBF in manic BP-I patients compared to euthymic BP-I patients and to HC during word generation task. - ↓ orbitofrontal cortex CBF in manic BP-I patients compared HC while at rest.	Various medications
Blumberg et al. 2000	11	- ↑ dorsal and right ventral anterior cingulate cortex, and left head of the caudate CBF in manic BP-I patients compared to euthymic BP-I patients.	Various medications
Rubinsztein et	6	- ↑ left dorsal anterior cingulate cortex CBF in manic BP I patients compared to HC while at	All male

Glucose Metabolism

Relative to BP II patients, limbic, frontal and parietal glucose metabolism has been reported to be increased in BP I patients (Ketter et al., 2001), while prefrontal glucose metabolism has been reported to be higher in manic BP I patients, relative to depressed BP II patients (Baxter et al., 1989). A decrease in cerebral glucose metabolism in the frontal lobes, however, is a common finding across studies of BP patients, regardless of state (Ketter et al., 2001; Al Mousawi et al., 1996; Baxter et al., 1989; Buchsbaum et al., 1986). In addition, BP II patients demonstrate a global decrease in glucose metabolism, compared to healthy controls (Ketter et al., 2001).

Four studies have compared cerebral metabolism in BP patients to MDD patients. Two of these found no statistically significant differences (Marangell et al., 1997; Baxter et al., 1989). In the third, BP patients differed from controls while MDD patients did not (Drevets et al., 1997), and in the fourth there was increased frontal lobe glucose metabolism in MDD patients compared to BP patients (Bachsbaum et al., 1986). See Table 1.2 for a review of cerebral metabolism findings in BP.

Table 1.2: Cerebral metabolism in bipolar disorder- literature review.

Summary of the data from single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroimaging studies to date, illustrating where there are increases (⇑), decreases (⇓), or no changes (⇔) in cerebral metabolism between specific therapeutic groups and healthy controls (HC). The table also indicates the number of patients (N) included in each study.

Glucose Metabolism (CMRglu)

Study	N	Findings	Notes
Buchsbaum et al. 1986	16	- ↓frontal lobe CMRglu in BP patients compared to MDD patients and HC. - ↓basal ganglia CMRglu in BP patients and MDD patients compared to HC. - ↔occipital lobe CMRglu between BP patients, MDD patients and HC.	Drug Free
Baxter et al. 1989	16	- ↑left dorsal anterolateral prefrontal cortex CMRglu in manic BP-I patients compared to depressed BP II patients. - ↔dorsal anterolateral prefrontal cortex CMRglu between depressed BP-II patients and MDD patients. - ↓dorsal anterolateral prefrontal cortex CMRglu in depressed BP-II patients and MDD patients compared to HC.	Drug Free
Al-Mousawi et al. 1996	25	- ↑left occipital cortex CMRglu in manic BP-I patients, depressed BP and MDD patients and patients with schizophrenia compared to HC. - ↓DLPFC CMRglu in manic BP-I patients, depressed BP and MDD patients and patients with schizophrenia compared to HC. - ↓left amygdala CMRglu in manic BP-I patients and patients with schizophrenia compared to HC. - ↓right temporal cortex CMRglu in manic BP-I patients and patients with schizophrenia compared to HC.	Various medications
Marangell et al. 1997	39	- Serum thyrotropin-stimulating hormone inversely correlated with CMRglu in patients with BP (I and II) and MDD. - ↔CMRglu between BP (I and II) patients and MDD patients, irrespective of gender.	Drug Free
Ketter et al. 2001	43	- ↔global CMRglu between BP-I patients and HC. - ↓global CMRglu between BP-II patients and HC. - ↓right lateral prefrontal cortex, right insula and right temporal pole absolute CMRglu in BP II patients and HC. - ↑medioposterior thalamus, left cerebellum, left lingular gyrus and left cuneus normalized CMRglu in BP-II patients and HC. - ↑cerebellum absolute CMRglu in BP-I patients and HC. - ↑cerebellum, lingular gyrus and cuneus normalized CMRglu in BP-I patients and HC. - ↔global or absolute regional CMRglu between BP-I patients and BP-II patients. - ↑supragenual anterior cingulate, right middle frontal gyrus and right inferior parietal lobule normalized CMRglu in BP-I patients compared to BP-II patients.	Drug Free

Functional Brain Activity (fMRI)

There do appear to be differences in regional activation between BP mood states, particularly in frontal (Malhi et al. 2004a; Malhi et al. 2004b; Blumberg et al. 2003a; Curtis et al. 2001), limbic (Strakowski et al. 2004; Mitchell et al. 2004; Malhi et al. 2004a; Caligiuri et al. 2003) and basal ganglia (Caligiuri et al. 2003; Blumberg et al. 2003b) regions.

Relative to HC, studies of regions in the frontal lobes and basal ganglia have consistently reported increased activation in depressed BP and euthymic BP patients [Strakowski et al. 2004; Malhi et al., 2004b; Lawrence et al. 2004; Blumberg et al. 2003; Caligiuri et al. 2003; Curtis et al., 2001). Increased activation has also been reported in temporal and limbic regions among depressed BP II patients (Malhi et al., 2004b). However, reduced temporal, limbic and frontal activation in depressed BP patients has also been reported (Mitchell et al., 2004).

To date there has only been one study that has compared bipolar patients with MDD patients (Lawrence et al., 2004). This study examined BP I patients who had no episodes of MDD in the previous 6 months (although most had some depressive symptoms at the time of the study), and found significantly increased activation in medial frontal cortex, ventromedial frontal cortex, dorsolateral and ventrolateral prefrontal cortex, thalamus, amygdala, uncus, hippocampus, and caudate/putamen in the BP I patients. See Table 1.3 for a review of fMRI data in bipolar disorder.

Table 1.3: fMRI in bipolar disorder- literature review.

Summary of the data from multiple studies in different patient groups. The table indicates the field strength of the magnet used, as well as the number of patients (N) included in each study. The summary of the data illustrates where there are increases (⇑), decreases (⇓), or no changes (⇔) in parameters being assessed between specific therapeutic groups and healthy controls (HC).

Study	Field Strength	N	Findings	Notes
Curtis et al. 2001	1.5T	5	- ↑superior medial parietal cortex, medial frontal cortex, cerebellum, right lingual gyrus and left inferior frontal gyrus activation in BP patients during verbal fluency compared to HC and patients with schizophrenia. - ↑lingual gyrus and right fusiform gyrus activation in BP patients during semantic decision making compared to HC. - ↑left lingual gyrus activation in BP patients during semantic decision making compared to patients with schizophrenia. - ↔frontal region activation between BP patients and HC, during semantic decision making task.	Lithium or Carbamazepine
Blumberg et al. 2003a	1.5T	36	- ↑rostral ventral prefrontal cortex activation in BP-I patients compared to HC, across mood states. - ↑left caudal ventral prefrontal cortex activation in depressed BP-I patients compared to euthymic BP-I patients. - ↓right ventral prefrontal cortex activation in manic BP-I patients compared to euthymic BP-I patients. - ↔dorsal anterior cingulate and prefrontal cortices activation between BP-I patients and HC, following Stroop task, across mood states.	Various Medications
Blumberg et al. 2003b		10	- ↑left putamen and thalamus activation in BP-I patients compared to HC, across mood states. - ↑ventral striatum activation with increasing depressive symptoms in BP-I patients.	Adolescents Various Medications
Caligiuri et al. 2003	1.5T	24	- ↑left external globus pallidus BOLD response in manic BP patients during reaction time task compared to depressed BP patients. - ↑right thalamus and right caudate BOLD response in depressed BP patients during right-hand reaction time task compared to manic BP patients. - ↑left external globus pallidus BOLD response with increasing manic symptoms BP patients. - ↓right external globus pallidus BOLD response with increasing manic symptoms BP patients. - ↑left internal and external globus pallidus, right thalamus left supplementary motor area, and right primary motor cortex BOLD response in unmedicated BP patients during reaction time task compared to HC. - ↑left primary motor area, right primary motor area, right supplementary motor area, and right thalamus BOLD response in unmedicated BP patients during left-hand reaction time task compared to medicated BP patients.	Various Medications
Malhi et al. 2004	1.5T	10	- ↑superior and middle frontal gyrus, superior temporal gyrus, lingual and subcallosal gyri, thalamus, hypothalamus and cerebellum right-sided activation in depressed BP-II patients compared to HC in response to negative vs. reference captioned pictures. - ↔frontal and temporal gyri activation between depressed BP-II patients and HC. in response to	Females Various medications

			negative vs. reference captioned pictures. - ↓cortical activation in depressed BP-II patients compared to HC in response to negative vs. reference captioned pictures. - ↑left medial and middle frontal gyrus, right inferior frontal gyrus, right thalamus, superior frontal gyrus, uncus, parahippocampal and fusiform gyri, and amygdala activation in depressed BP-II patients compared to HC in response to positive vs. reference captioned pictures. - ↑overall activation in depressed BP-II patients compared to HC in response to positive vs. reference captioned pictures. - ↑middle and inferior frontal gyri, right superior frontal gyrus, right parahippocampal gyrus, right posterior cingulate, right inferior parietal lobule, right thalamus, medial globus pallidus and left insular cortex activation in depressed BP-II patients compared to HC in response to positive vs. negative captioned pictures. - Only depressed BP-II patients showed subcortical brain activation, across experimental conditions.	
Malhi et al. 2004	1.5T	10	- ↑left caudate, left thalamus and right superior frontal gyrus activation in hypomanic BP-II patients compared to HC in response to negative vs. reference captioned pictures. - ↔superior frontal gyrus activation between hypomanic BP-II patients and HC, in response to negative vs. reference captioned pictures. - ↓overall cortical activation in hypomanic BP-II patients compared to HC in response to negative vs. reference captioned pictures. - ↑left inferior parietal lobule, sypramarginal gyrus, and superior and middle frontal gyri activation in hypomanic BP-II patients compared to HC in response to positive vs. reference captioned pictures. - ↑superior and middle frontal gyri, pre- and post-central gyri, inferior parietal lobule, right cuneus, and precuneus activation in hypomanic BP-II patients compared to HC in response to positive vs. negative captioned pictures.	Females Various medications
Mitchell et al. 2004	1.5T	11	- ↓amygdala, uncus, bilateral superior temporal gyrus, and right inferior frontal gyrus activation in BP patients compared to HC in response to pure emotional prosody. - ↓right anterior middle temporal gyrus activation in BP patients compared to patients with schizophrenia in response to pure emotional prosody. - ↑right posterior middle temporal gyrus activation in BP patients compared to patients with schizophrenia in response to pure emotional prosody. - ↓bilateral superior temporal gyrus, and left middle temporal gyrus activation in BP patients compared to patients with schizophrenia in response to emotional prosody in normal speech. - ↑lateral and anterior superior temporal gyrus activation in BP patients compared to patients with schizophrenia in response to emotional prosody in normal speech.	Various medications
Lawrence et al. 2004	1.5T	12	- ↑right globus pallidus/anterior thalamus activation in euthymic BP-I patients compared to MDD patients and HC in response to mild fear.	Various medications

			- ↑left medial prefrontal cortex activation in euthymic BP-I patients compared to MDD patients in response to mild fear. - ↓right amydala/hippocampus and right dorsolateral prefrontal cortex activation in euthymic BP-I and MDD patients compared to HC in response to mild fear. - ↑left amydala and ventrolateral prefrontal cortex activation in euthymic BP-I patients compared to MDD patients and HC in response to intense fear. - ↑right globus pallidus/anterior thalamus activation in euthymic BP-I patients compared to MDD patients in response to intense fear. - ↑left uncus, amygdala, caudate/putamen, and ventromedial prefrontal cortex activation in euthymic BP-I patients compared to MDD patients and HC in response to mild happiness. - ↓right parahippocampal gyrus, thalamus, midbrain, caudate nucleus, and left amygdala activation in euthymic BP-I and MDD patients compared to HC in response to intense happiness. - ↑right ventral and dorsolateral prefrontal cortex activation in euthymic BP-I patients compared to MDD patients in response to intense happiness. - ↑left hippocampus and left ventral prefrontal cortex activation in euthymic BP I patients compared to MDD patients and HC in response to mild sadness. - ↓orbitofrontal cortex, and right dorsolateral prefrontal cortex activation in euthymic BP-I patients compared to HC in response to mild sadness. - ↓right putamen activation in euthymic BP-I patients compared to MDD patients and HC in response to mild sadness. - ↑right ventral prefrontal cortex and right anterior cingulate gyrus activation in euthymic BP-I patients compared to MDD patients and HC in response to intense sadness. - ↓ dorsolateral prefrontal cortex activation in euthymic BP-I and MDD patients compared to HC in response to intense sadness. - Medication acted to normalize neuronal responses in BP-I and MDD patient groups.	
Strakowski et al. 2004	3.0T	10	- - ↑hypothalamus, left insula, left parahippocampus/amygdala, left ventral prefrontal cortex and visual associated cortex activation in euthymic BP-I patients compared to HC during a continuous performance task. - ↓left fusiform gyrus and left medial frontal cortex activation in euthymic BP-I compared to HC during a continuous performance task. - ↑right inferior frontal cortex and ventrolateral frontal cortex activation with increasing task performance in euthymic BP-I patients.	Drug Free
Caligiuri et al. 2004	1.5T	18	- Longer reaction times in manic BP-I patients compared to HC during a simple reaction time task. - Longer reaction times in depressed BP-II patients compared to HC and manic BP-I patients during a simple reaction time task.	Various Medications

			- ↑left hemispheric asymmetry in the primary motor area in manic BP-I and depressed BP-II patients compared to HC during right hand trials. - ↓hemispheric asymmetry in the primary motor area in manic BP-I patients compared to depressed BP-II patients during left hand trials. - ↔hemispheric asymmetry in the supplementary motor area between depressed BP-II patients and HC. - ↓right hemispheric asymmetry in the supplementary motor area in manic BP-I patients compared to depressed BP-II patients and HC during left hand trials. - ↓primary motor area BOLD response in manic BP-I and depressed BP-II patients treated with antipsychotics or mood stabilizers compared to unmedicated patients. - ↔left-right primary motor area hemispheric asymmetry between depressed BP-II patients and HC, across task and response hand. - ↑right hemispheric asymmetry in the primary motor area in manic BP I patients compared to HC for right hand simple reaction time trials. - ↓primary motor and supplementary motor areas contralateral hemispheric asymmetry in manic BP-I and depressed BP-II patients treated with antipsychotics or antidepressant compared to unmedicated patients.	

There are significant issues when drawing inferences from the literature on functional-metabolic studies of brain function. In particular, differences in image acquisition and task performance mean that there is limited ability to compare and contrast studies. The results of one study only become supportive of another when the images are acquired in a similar fashion and give information about a similar domain of brain function. Thus, while one study may find increased amygdala activation, another may find decreased amygdala activation in response to a different task. These may not necessarily be contradictory findings, but instead may suggest task-specific alterations in amygdala activation. Additionally, Almost all studies to date have examined only small numbers of patients, varying in size from 2 – 26 patients.

There have also been different patient groups examined, with variable mixes of BP I and BP II patients, presenting with differing levels of illness severity, duration, and treatments. Finally, different studies have used different descriptions for the areas that are affected, with some groups using large area descriptions (such as "frontal cortex"), while others are more specific (such as "dorsolateral prefrontal cortex").

All these factors indicate that current results should be analyzed in the context of the specific literature of the type of task and brain activity being explored.

1.3 Neuropsychology of Mood Disorders

1.3.1 Neuropsychological impairment in unipolar depression

It is well established that patients suffering from major depressive disorder show deficits in performance on tests of several domains of cognitive function (Porter et al., 2007). Neuropsychological batteries in patients who are symptomatic and asympotomatic have been applied in the hopes of clearly defining the state and trait neurocognitive deficits expressed. It has even been suggested that neuropsychological improvement is an effective endpoint to judge effectiveness of antidepressive drug therapies (Gallagher et al., 2007).

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is widely used to assess neuropsychological function across a wide range of cognitive domains. In 1996, Elliott et al. compared twenty-eight patients with major depressive disorder to twenty-two age-matched healthy subjects on the CANTAB battery. Depressed patients demonstrated significant deficits along almost all domains tested, including in visual memory, spatial working memory and planning. In earlier studies, Austin et al. (1992) also documented deficits in depressed patients on short term memory, recognition and recall and in attention and cognitive set shifting. A later study (Austin et al., 1999) confirmed a mnemonic deficit in depression and suggested the presence of set shifting difficulties and psychomotor slowing in melancholic depressed patients tested across a wide battery of cognitive domains.

Specifically, with regard to memory and attention, one study has shown that depressed patients perform over 1.5 standard deviations worse than healthy controls when tested on working memory and attention tasks and only slightly better (one standard deviation) on a test of verbal long term memory (Landro et al., 2001). Some (Nebes et al., 2000; Beats et al., 1996; Elliott et al., 1996), but not all (Purcell et al., 1997; Barch et al., 2003) studies have suggested the presence of a working memory deficit in depressed patients. It should be noted, however, that any mnemonic deficit that has been observed in depressed patients is of episodic or explicit memory function and not implicit memory (Sweeney et al., 2000; Hertel and Hardin, 1990). Reviews of the literature support the presence of mnemonic and attention deficits in depression (Gualtieri et al., 2006; Austin et al., 2001). The fact that there is not one consistent memory deficit observed across all studies is likely because age, severity of depression as well as comorbidity can all influence the degree of neurocognitive impairment (Gualtieri et al., 2006).

Symptoms of psychomotor slowing and reduced motor behavior are commonly observed, in depressed subjects. It seems reasonable to expect that depressed patients will desmonstrate a specific neuropsychological deficit in psychomotor speed. In fact, even in simple line drawing tests, depressed patients show a significantly longer reaction time (961 ms) compared to healthy subjects (758ms) (Sabbe et al., 1996). This psychomotor slowing becomes worse as the complexity of the tasks increases (Sabbe et al., 1996). Poor psychomotor performance on simple motor tasks in depression was confirmed several years later, as Sabbe and colleagues (1999) observed an overall slowing of motor behavior (longer movement durations, longer pauses and lower motor speed) in depressed inpatients. Depressed patients are also slower than controls in motor performance on more complex tasks (Ilsley et al., 1995; Beats et al., 1996; Purcell et al., 1997). Psychomotor slowing has been shown in young patients with depression, and so should not be considered to be an entirely age-related deficit (Purcell et al., 1997). In addition, Pier et al. (2004) did not observe psychomotor slowing in a group of dysthymic patients compared to their more severe major depressive disorder counterparts.

Although not as severe as in schizophrenic patients, executive function deficits are also present in depressed patients (Gualtieri et al. 2006). Performance in this domain is considered an assessment of problem-solving, response inhibition, planning abilities, and a subject's use of feedback to modulate response (Gualtieri et al., 2006). To objectively measure executive function performance, subjects engage in differing tasks including the Stroop test, the Wisonsin Card Sorting Test (WCST), the Tower of London (TOL), the Trail Making Test (part B) (TMT-B) and the Controlled Oral Word Association Test (COWAT) (see Ottowitz et al., 2002 for a full review of these tests). Reviewing the literature prior to 2002, almost all studies employing the Stroop test, the WCST and the TOL test demonstrated impairments in unipolar depressed patients (Ottowitz et al., 2002). However, there is less consistency in the findings from unipolar patients tested on the TMT-B, where there are no positive findings, or the COWAT of verbal fluency, where there are only two positive findings of deficit in depressed patients (Ottowitz et al., 2002). Since 2002, the results of verbal fluency testing in depressed patients remains inconclusive, with some researchers observing deficits (Okada et al., 2003; Audenaert et al., 2003) and some not (Matsuo et al., 2002; Harvey et al., 2004). In their recent assessment of twenty-two depressed inpatients, Harvey and colleagues (2004) also found an increase in perseverative errors on the WCST in the patient group, an increased reaction time for patients completing the TMT-B and an increase in processing time on the Stroop test.

In remitted or asymptomatic depressed patients, two studies describe the deficits observed. Weiland–Fiedler et al. (2004) found, in their application of CANTAB tests, that patients still demonstrated deficits in sustained attention, working memory and psychomotor speed, even unmedicated. A study by Paelacke-Habermann et al. in 2005 also showed that remitted patients (from severe depression), had maintained deficits in tests of attention and in executive function. See Table 1.4 for a summary of executive control deficits in major depression.

Table 1.4: Studies of executive function in patients with major depressive disorder.

COWAT, Controlled Oral Word Association Test; BD/d, Bipolar Disorder, depressed state; DI, patients with major depressive disorder demonstrated impairments relative to controls; MDD, major depressive disorder; MDE, major depressive episode; NS, subjects did not demonstrate a statistically significant difference relative to normal controls; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test. Adapted from Ottowitz et al. (2002).

Test	*Study*	*Diagnosis*	*Finding*
Stroop	Degl'Innocenti et al. (1998)	"Major depressive syndrome"	DI, slower performance
	Lemelin et al. (1998)	MDE	DI, only in subgroup with psychomotor retardation
	Paradiso et al. (1997)	MDD, BD/d	DI
	Lemelin et al. (1997)	MDE	DI, higher interference
	Lemelin et al. (1996)	MDE, BD/d	DI, slower performance and higher interference
	Trichard et al. (1995)	MDE	DI
WCST	Grant et al. (2001)	MDD	DI on 5 of 6 measures
	Fossati et al. (1999)	MDD	NS
	Merriam et al. (1999)	MDD	DI on 7 of 8 measures
	Degl'Innocenti et al. (1998)	"Major depressive syndrome"	DI on 4 of 11 measures
	Martin et al. (1991)	MDD	DI on 3 of 8 measures
	Jones et al. (1988)	MDE	DI
Tower of London	Purcell et al. (1997)	MDD	DI on 1 of 6 measures
	Elliott et al. (1997)	MDD	DI, performance accuracy
	Watts et al. (1988)	MDD	DI on 3 of 6 measures
TMT, Part B	Grant et al. (2001)	MDD	NS
	Channon et al. (1993)	MDD	NS
COWAT	Grant et al. (2001)	MDD	NS
	Fossati et al. (1999)	MDD	DI on semantic fluency only
	Degl'Innocenti et al. (1998)	"Major depressive syndrome"	DI
	Ilsley et al. (1995)	MDD	NS
	Smith et al. (1994)	MDD	NS
	Jones et al. (1988)	MDE	NS
	Wolfe et al. (1987)	MDD	NS

1.3.2 Neuropsychological impairments in bipolar disorder

It may be more difficult to characterize the neurocognitive deficits present in BP. While unipolar subjects tested for neuropsychological function are often medicated, which could confound results, there are additional challenges in assessing bipolar patients. First, there is a wider collection of medications used in the treatment of BP, and patients are often on more than one medication, making treatment effects difficult to tease out (Murphy et al., 2001). Secondly, studies often fail to distinguish or separate patients who are in different states of the illness, or who suffer from BP II and BP II. This means that many studies have observed patients in both BP I and BP II together, and across manic, depressed, hypomanic and euthymic states (Murphy et al., 2001). It is to be expected that these factors have limited any overwhelming consensus among neuropsychological findings in BP.

In euthymic patients, neuropsychological deficits have been observed in tests of executive function, verbal memory, sustained attention, psychomotor speed, verbal fluency and working memory (see Savitz et al., 2005 for a full review). Two recent examinations of neuropsychological function by Martinez-Aran et al. (2005, 2007) have shown that euthymic bipolar patients have difficulties performing on the WCST (increased perseverative errors), the TMT part A (attention and working memory), tests of verbal fluency, and tests of verbal declarative memory. Another group, van Gorp et al. (1998) have previously observed a deficit in verbal memory in a group of euthymic patients, and additionally observed an increased number of perseverative errors on the WCST in bipolar euthymic patients with prior alcohol dependence. It also appears that, akin to unipolar depression, any memory deficit in BP is declarative, or explicit, while implicit memory remains unaffected (van Gorp et al., 1998).

In studies where patient groups are varied, containing depressed, manic, mixed episode, and euthymic patients, neuropsychological findings still demonstrate a significant deficit along many domains. Bipolar patients show deficits in verbal memory, verbal fluency, attention, working memory and psychomotor speed (Basso et al., 2002; Gourovitch et al., 1999). This can be contrasted with those studies that have examined bipolar patients in one state only. Manic patients exhibit a range of deficits including pattern, spatial and visual memory (Murphy et al., 1999) as well as executive function (Stroop test, McGrath et al., 1997). Earlier examination by Hoff et al. (1990) even suggested that bipolar patients in a manic state could not be differentiated based on neuropsychological assessment of verbal memory, visuospatial memory, executive function, and psychomotor speed from a sample of schizophrenic patients, who have generally been considered to have a severe neuropsychological deficit. Separated from other types of patients, assessment of bipolar patients in a depressed state reveals deficits in verbal fluency and verbal memory, compared to healthy controls (Wolfe et al., 1987).

Over the last several years, however, a number of studies have accumulated comparing the cognitive deficits observed across bipolar patients in the depressed, manic and euthymic phases. The findings from these studies may assist in clarifying the range of state related cognitive deficits observed in the illness. In a comparison of depressed and euthymic bipolar patients, Martinez-Aran and colleagues (2002) described deficits in both patient groups in declarative verbal memory and executive function (TMT-B) tasks, but found that the depressed patients were also deficient in a task of verbal fluency. These results were in agreement with a more recent study which demonstrated that patients who are manic (or hypomanic), depressed or euthymic show verbal memory and executive function deficits (Stroop, WCST), while depressed patients show more extensive deficits in executive function (TMT-B) and deficits in verbal fluency (Martinez-Aran et al., 2004). Malhi et al. (2007) have also suggested that depressed bipolar patients display more verbal fluency, executive function and psychomotor speed deficits than euthymic patients, although they note that verbal memory deficits seem to persist across the depressed, euthymic and hypomanic phases of the illness.

Finally, the neuropsychological differences between BP I and BP II are still largely unclear. However, in one recent study an assessment of euthymic BP I and BP II patients' performance on a range of neurocognitive domains has revealed differences between these groups. Both BP I and BP II patients perform poorly compared to healthy controls in attention and working memory, and also show a trend towards increased perseverative errors in the WCST. Nonetheless, the performance of bipolar II patients on most measures was between that of BP I patients and healthy controls (Torrent et al., 2006). The authors suggest that BP II patients demonstrate an intermediate level of impairment contrasted with healthy subjects and BP I patients.

Neuropsychological function: bipolar disorder vs. unipolar disorder

There are few studies to date which have directly examined the neurocognitive impairments in bipolar patients compared to unipolar depressed patients. For the most part, these have investigated bipolar patients in a depressed state contrasted with symptomatic unipolar patients. In the domain of memory function, it has been observed that bipolar depressed patients suffer significant deficits on verbal memory and verbal fluency, compared to unipolar depressed patients (Wolfe et al., 1987). In fact, Wolfe et al. (1987) found no difference between the verbal memory and fluency impairments observed in bipolar depressed patients and a group of patients suffering an early stage of Huntington's disease. In contrast, however, other studies have found no significant differences between bipolar depressed and unipolar depressed patients on verbal memory (Bearden et al., 2006), or on working memory, psychomotor speed and executive function (Sweeney et al., 2000). However, depressed patients were impaired relative to controls (Bearden et al., 2006) and mixed/manic bipolar patients demonstrated poorer working memory than nonbipolar depressed patients (Sweeney et al., 2000). In a comprehensive study of executive function tasks, Borkowska and Rybakowski (2001) found that bipolar depressed patients performed significantly worse on the Stroop test, verbal fluency test, and made significantly more perseverative errors and completed fewer categories on the WCST than unipolar depressed patients, with an equal mean intensity of depression.

1.3.3 Neuronal mechanisms of executive function

Executive function tasks, or executive control tests, may be defined as complex cognitive problems requiring the coordination of behavior to problem-solve, modulate, and execute a plan to achieve a goal (Ottowitz et al., 2002; Elliott, 2003). Solving executive control problems requires the ability to monitor information in the external world, use long term and working memory to obtain problem-related information, engage behavioral inhibition of incorrect responses, use feedback to modulate responses, and enagage in mental shifting of sets and strategies (Ottowitz et al., 2002; Funahashi 2001). Ultimately, executive function cannot be considered to refer to one single concept of cognition, but rather to a set of processes and the ability to use these successfully to complete a complex task (Elliott, 2003).

Executive function, therefore, subserves many of the skills used in problem solving and daily functioning at work and at home. However, in the clinical setting, executive function is assessed by neuropsychological examination with a battery of cognitive tests. These include the Stroop test that requires that subjects shift mental sets from color naming to word naming, the TOL test that requires spatial problem solving techniques, the WCST that requires mental set shifting and problem solving based on feedback, and the COWAT that tests verbal fluency. In patient groups, evaluation of performance on these tests, as well as the numbers and types of errors made, can indicate if executive function impairments are present in the illness.

Cumulative data obtained in brain-lesioned patients and in functional imaging studies in healthy subjects has lead to theories of prefrontal cortex command of executive function. Researchers have observed difficulties in planning and decision-making, as well as impaired judgment in patients with prefrontal cortex damage (Funahashi, 2001; Elliott 2003). In addition, patients with prefrontal cortex damage show impaired performance on a range of executive control tasks (Elliott et al., 2003). The results of these findings led researchers to hypothesize that executive function requires intact function of the frontal lobes.

With the advent of neuroimaging, the neural substrates of executive task performance began to be elucidated in healthy subjects. Regional blood flow in healthy subjects is markedly increased in the right anterior cingulate and frontal lobe during performance of the Stroop test (Bush et al., 2000; Bench et al., 1993; Pardo et al., 1990), and in the dorsolateral prefrontal cortex (DLPFC), inferior parietal lobe, and inferior temporal lobe, during execution of the WCST (Berman et al., 1995). Similarly, carrying out the TOL task causes activation of the DLPFC, parietal cortex, anterior cingulate and occipital cortex (Drewe et al., 1974), while verbal fluency causes increased activity in the inferior prefrontal lobe, and left medial temporal and superior parietal lobe (Pihlajamaki et al. 2000). In fact, Elliott (2003) describes three main clusters of activations which are found in executive function task completion: the dorsal anterior cingulate, mid dorsolateral and mid ventrolateral regions. It has also been suggested that underlying components of executive function are localized to specific regions within the prefrontal cortex. The generation of executive function control and problem solving includes an extensive use of working memory strategies to maintain, mediate and modulate information. Some researchers maintain that the mechanism of working memory itself seems to be separately controlled within the DLPFC and VLPFC. In this case, the VLPFC gathers representations obtained by the posterior cortex and the DLPFC controls the monitoring and modulation of these representations (Elliott, 2003).

While functional imaging studies to date point to the prefrontal cortex as a governing site of action for executive function control (Ottowitz et al., 2002), underlying these functions is suggested to be the intact communication of prefrontal and subcortical circuits, composed of a loop between prefrontal regions and the striatum mediated by the thalamus, and globus pallidus (Elliott 2003; Ottowitz et al., 2002). Disruptions of the striatal circuit also result in deficits in executive function, as evidenced in patients with Parkinson's disease (Elliott et al., 2003), and cause deficits that liken to prefrontal cortical damage in animals (Divac et al., 1994).

It is clear that executive function is a complicated form of cognition requiring intact neural systems to coordinate multiple sub-processes to solve complex problems.

*1.4 **Functional Magnetic Resonance Imaging (fMRI)** (Huetel et al., 2006)*

Over the last decade, from its initial use as a method of assessing brain structure, magnetic resonance imaging (MRI) has evolved to allow the evaluation and measurement of brain function by means of functional MRI (fMRI). The establishment of the fMRI signal as a tool to assess brain function was a significant advancement in the field as previous methods used to quantify brain function were more invasive (positron emission tomography (PET) and single photon emission computed tomography (SPECT)) and were limited by poor spatial (electroencephalogram (EEG) and/or temporal resolution (PET and SPECT). Instead, by noninvasive application of magnetic fields, fMRI acquires a signal with good spatial and temporal resolution reflecting brain activation.

In order to assess brain function, fMRI takes advantage of the magnetic properties of oxygenated and deoxygenated blood intertwined in the hemodynamic response that occurs when the brain becomes engaged in a task. fMRI does not image neural activity *per se*, but rather physiological processes which are correlated with neuronal activation. In fact, it is still unclear what component of neural activation is reflected in the fMRI signal.

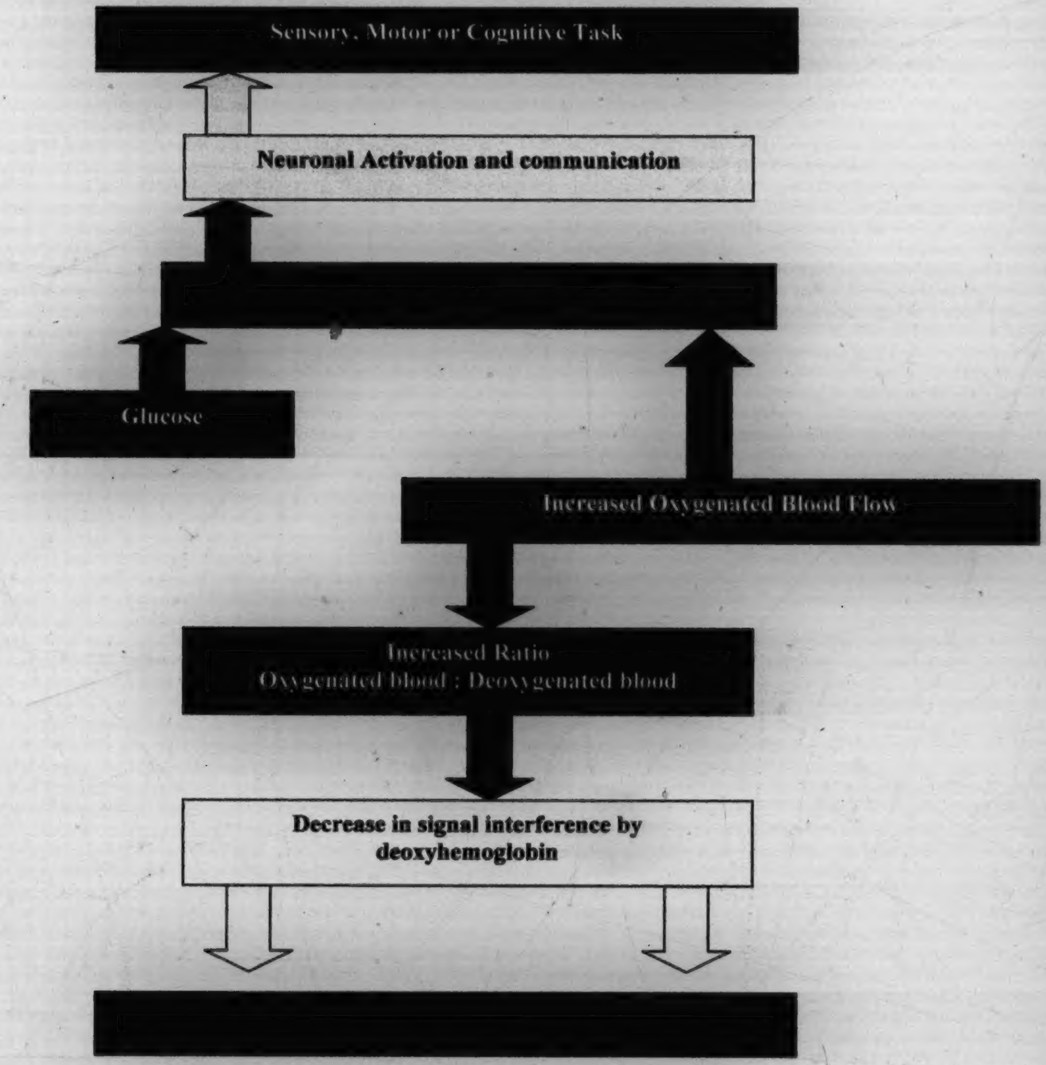
As the brain engages in cognitive, sensory, or motor processes, the activity of neurons in specific brain regions increases. This increase in activity creates a greater need for energy by neurons, which is achieved by the conversion of glucose to energy and is accompanied by an increase in oxygenated blood flow to the area. An increase in oxygenated blood flow to areas of brain activity is crucial because it is this factor which will cause a measurable change in the acquired signal between areas of the brain which are activate and inactive. For this reason we call the signal acquired in fMRI the blood-oxygen level dependent (BOLD) response. See Figure 1.1 for a depiction of this process.

As an excess amount of oxygenated blood is recruited to areas of activity, the ratio of oxygenated blood to the once predominant deoxygenated blood in this region begins to increase. As this ratio increases, the effect of deoxygenated hemoglobin causing magnetic suppression of the fMRI signal is released and the acquired signal in areas of brain activation is measured to be larger (on the order of 0.5- 2%). The BOLD signal amplitude will approach its largest in sensory brain regions when the subject is engaged in sensory tasks and will weaken as tasks becomes more complex and areas of higher cognitive function are used.

The following sections characterize some of the developmental challenges and solutions in designing and implementing an fMRI study. These will be discussed in three sections; paradigm design, imaging parameter selection based on spatial and temporal resolution, and data analysis.

Figure 1.1: The relationship between the fMRI BOLD signal and the task performed.

This figure is adapted from Figure 6.1 of Huetel et al., (2004)


Sensory, Motor or Cognitive Task
Neuronal Activation and communication
Glucose
Increased Oxygenated Blood Flow
Increased Ratio
Oxygenated blood : Deoxygenated blood
Decrease in signal interference by
deoxyhemoglobin

1.4.1 Paradigm Design

In the fMRI study, the goal is to have subjects engage in tasks and acquire the change in BOLD signal in areas activated by the test. A viewing system is set up in order to present the tasks and instructions to participants while in the MRI scanner. This may include requiring participants to wear projection goggles or require the set-up of a projector screen within the magnet, capable of being viewed while lying down.

There are two main types of experimental design that are applied in fMRI; blocked design presentations and event-related design presentations. See Figure 1.2 regarding block and event-related paradigm design.

Blocked Design Paradigms

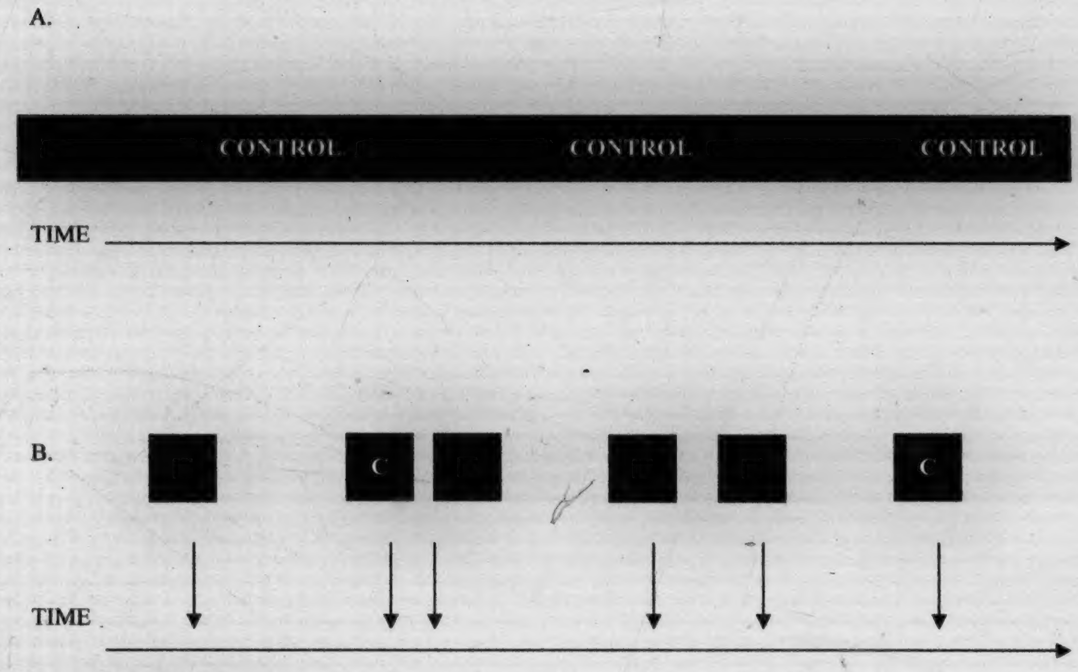
The goal of the blocked design paradigm is to assess a change in the dependent variable (BOLD signal) between an *active* and *control* task presented in alternating blocks. In this scenario, the *active* task should engage the subject in the function of interest while the *control* task accounts for any additional processes *not* of interest which are also engaged in the *active* task. This means that any change in the BOLD signal obtained by a subtraction of the signal in the *control* task from the signal obtained in the *active* task, will reflect the brain activation during the mental process of interest. Blocks in this design will alternate between performance of the *active* task and the *control* task, and block length will vary depending on the task of interest. Tasks where the process of interest is modulated quickly (e.g. Finger tapping) may use short blocks (30 sec per active and control conditions) while tasks where processing is more complex (e.g. executive function) may use longer blocks (50sec per active and control condition). The idea is to increase the number of time points and maximize the measurement of the change in signal which is assessed by a sum of all time points in all blocks of one condition, over the other, without adding confounding factors into the design or increasing the variability within the conditions. The blocked design paradigm is a very effective study design for the **detection** of activation. Using a blocked design you will obtain a sensitive measurement of what regions of the brain are more activated by the *active* task than the *control* task. You will not, however, be able to estimate the time course of brain activity using a block design.

Event-Related Design Paradigms

In the event-related design, the main assumption is that neural activity brought on by engagement in a task results in short and discrete periods of activation in brain regions. In this case, the task of interest (the event) is presented as a short singular stimulus separated in time (2sec-20sec) from another event. Event-related designs measure the transient changes in signal that occur with exposure to one stimulus. This allows the measurement of the hemodynamic effect of the brain response to one stimulus. The advantage of an event-related design is that it allows measurement of the change in signal **across time** with brain activity to the experimental condition.

Figure 1.2: Paradigm design in fMRI experimentation.

A) A Block design study will alternate between two tasks, one active task and one control task. B) An event-related design presents a single stimulus over time separated by an interstimulus interval.


A.
CONTROL
CONTROL
CONTROL
TIME
B.
C
C
TIME

Where ■ and C represent an active task event and a control task event, respectively.

The best paradigm for each particular fMRI study will be decided based on an assessment of the goals of the experiment, detection or estimation, combined with an understanding of how the process of interest is engaged mentally.

1.4.2 Acquisition parameters; spatial and temporal resolution of fMRI

A second consideration in the implementation of an fMRI experiment is selecting imaging parameters that will optimize the goals of the study in terms of obtaining the best spatial and temporal resolution of the signal. A high spatial resolution means that signal in different locations in the brain will be easily distinguished within an image, while a high temporal resolution means the signal will be measured frequently, resulting in the ability to distinguish the signal at very short intervals.

The BOLD signal effect occurs based on a modulation of the signal obtained using nuclear magnetic resonance (NMR) methods. Essentially, applying a magnetic field causes protons to line up and precess in the direction of the external magnetic. Applying a second brief magnetic pulse casues the protons to precess in unison and creates a net magnetization in the horizontal plane. After removal of the applied pulse, the protons both; 1. begin to precess at slightly different frequencies because of internal field inhomogeneities (i.e. BOLD effect), and 2. regain magnetization in the original longitudinal plane. In the case of fMRI, the hemodynamic response in active brain regions influences the speed at which protons loose precession unison, and this results in an increased signal in these areas. We have a great deal of influence, however, in modulating the signal's capacity for spatial and temporal resolution by modulating how the signal is acquired, the parameters of the scanning experiment.

Spatial Resolution

If the ability to distinguish the signal between two very close locations in the brain fits the goals of the experiment, a high spatial resolution is needed. The spatial resolution of the signal will be regulated by the size of the voxels (sampling volumes) imaged in the experiment. The size of the voxel is determined by the desired field of view (total imaging volume), the matrix size (how many voxels in each dimension) and the slice thickness. Ideally, the smaller the voxel of information acquired, the greater the spatial resolution, or the greater ability to see fine distinction between the signal in different brain regions. However, there are two large disadvantages of using small voxels to acquire the signal. As the voxel size decreases so too does the ability to detect the signal in individual voxels; in addition, this increases the time needed to acquire the signal (resulting in decreased temporal resolution). Additionally, acquiring images with a high spatial resolution in fMRI can result in distortions in the signal over time. Because the BOLD signal decays very quickly, acquiring more voxels in one volume will result in a difference in signal strength over time from the first voxel acquired through to the last. If there are many tiny voxels then the signal detected will be markedly different between early and late acquired voxels.

One can circumvent some of the problems in using small voxels if a stronger static magnetic field is used (e.g. 4 Tesla instead of 1.5 Tesla) to acquire the signal. As the static field gets larger, it increases the raw signal-to-noise ratio increasing the signal change in areas of activity. At each voxel, this increased signal means detection is possible with smaller volumes, and improves spatial resolution. However, acquiring the signal with stronger magnets also carries disadvantages. Particularly relevant in functional imaging is the fact that higher magnet field strengths, while resulting in higher raw signal-to-noise, also amplify physiological noise that may be present. Alterations of the signal because of head motion, swallowing, heart rate, or other physiological processes are increased with high magnetic field strength, resulting in an overall decrease in functional signal-to-noise. High field strengths may also increase artifacts in the signal, particularly at air-tissue boundaries.

For most fMRI experiments, there is a compromise made in order to optimize spatial resolution. Typically this means that a whole brain functional imaging experiment uses 4-5mm^3 voxels to acquire the signal, compared to the very high spatial resolution of an anatomical scan which obtains voxels 1mm in each plane.

Temporal Resolution

The ability to image the timing of brain activation to within the shortest intervals means that the signal obtained has a high temporal resolution. In fMRI, the maximal temporal resolution possible allows the discrimination of events separated by intervals in the order of seconds. Acquiring the signal in more time points during the experiment increases temporal resolution. This is accomplished by decreasing the *time to repetition* (TR), which represents the time to acquire one full volume (image). However, if the TR is decreased beyond a point, there is a detrimental effect on the detection of the signal. Additionally, a compromise is required between gaining a very high temporal resolution and adequate spatial resolution. Scanners are limited in the amount of slices which can be acquired per second, resulting in a tradeoff, an image with very high temporal resolution, but low spatial resolution (large voxels).

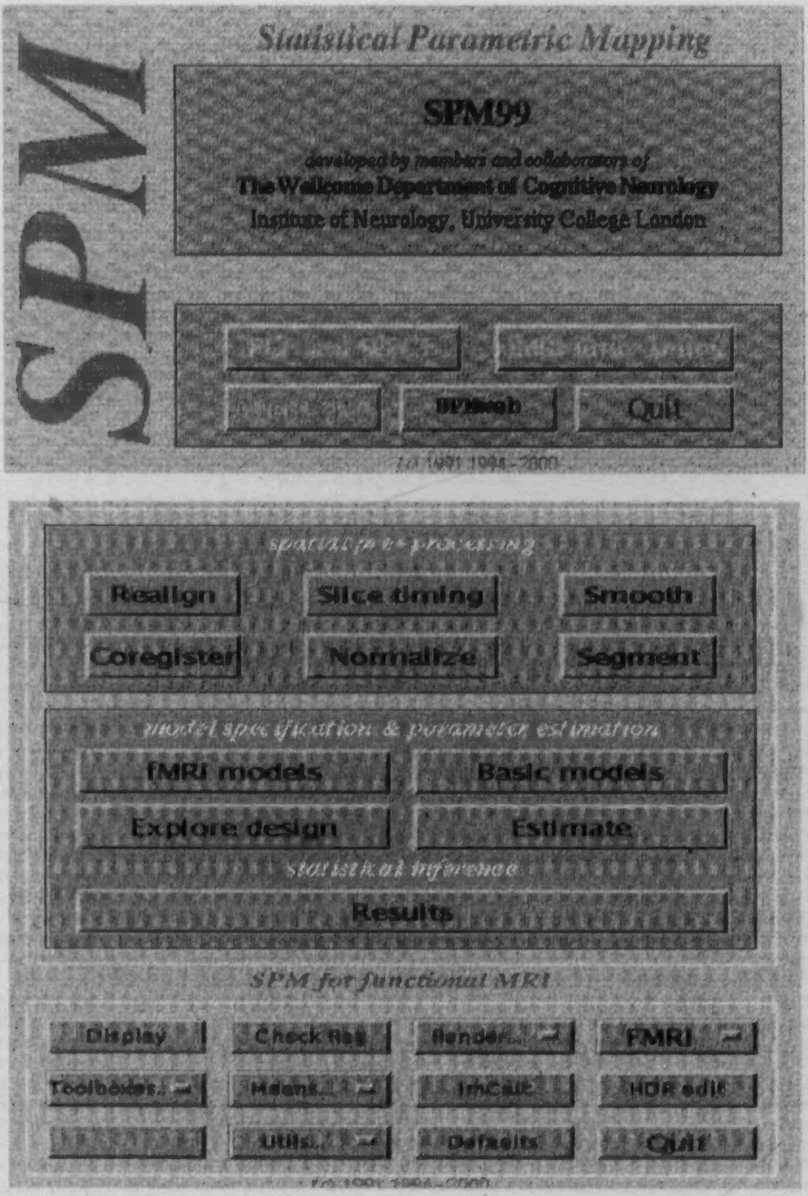
The tradeoff between temporal and spatial resolution must again be reconciled by an assessment of the experimental goals. Is it in the interest of the investigation to have high detection power across the whole brain or does the research attempt to answer questions about the timing of more specific regional events? The answers to the questions will help to determine the best imaging parameters to be applied in the study. A last consideration that plays a role in these decisions is the time constraints of the study. The time needed to acquire the images will increase as a greater resolution is desired (either spatial or temporal). The time needed to acquire a scan should be taken into account in designing the experiment, particularly with patient populations who may fatigue easily or find it difficult to concentrate for long periods of time.

1.4.3 Data Analysis

fMRI data analysis requires a statistical assessment of the change in signal (active task – control task) at each voxel acquired in imaging, over the course of all time points acquired in each task. Several software programs have been developed to perform the highly complex statistical functions of making so many comparisons. These include the Statistical Parametric Mapping (SPM) software (See Figure 1.3) by the Wellcome

Imaging Group at the University College of London, the Analysis of Functional NeuroImages (AFNI) software developed at the University of Wisconsin, and the BrainVoyager software by Brain Innovation Inc. Each software program, however, at its core should share the same functions- preprocessing including head motion correction, normalization and smoothing, and a statistical analysis tool.

Figure 1.3: Screenshots of Statistical Parametric Mapping (SPM99) software workspace.


SPM
Statistical Parametric Mapping
SPM99

developed by members and collaborators of
The Wellcome Department of Cognitive Neurology
Institute of Neurology, University College London

SPMweb
Quit
(c) 1991 1994 - 2000
spatial pre-processing
Realign
Slice timing
Smooth
Coregister
Normalize
Segment
model specification & parameter estimation
fMRI models
Basic models
Explore design
Estimate
statistical inference
Results
SPM for functional MRI
Display
Check Reg
Render...
FMRI
Toolboxes...
Means...
ImCalc
HDR edit
Utils...
Defaults
Quit
(c) 1991 1994-2000

Preprocessing

Preprocessing of the original data acquired from the scanner is necessary to prepare for legitimate statistical analysis. Information from the scanner regarding the MR signal at each voxel at every time point is reconstructed into images of the signal in each volume at every time point. Therefore, the data of each task are contained within a series of images, each a time point and each composed of one acquired volume of information. Preprocessing takes place in three essential steps; head motion correction, normalization and smoothing.

Head motion correction:

It is important to correct for even small changes in head position that have occurred over the course of the experiment because of shifts in body position or movements of the head. If the subject has moved considerably, the time series for a particular location will be cross contaminated with that of another location, and statistical differences may no longer be detectable as it is assumed that each voxel is independent from the others. In motion correction, every volume is adjusted to reflect the same position of the head. This is accomplished by a calculation of parameters required to maintain a rigid body transformation of all the volumes. The set of parameters (along x and y axes and in rotation plane) that most closely allows the image from each volume to line up to the first is used to *realign* each successive volume.

Normalization:

The large amount of variability in brain size and topography between individuals requires that a transformation be performed to allow comparison between subjects, and also to allow reference to a common stereotactic space. The goal of spatial normalization is to compensate for these differences in brain size and shape by transforming each set of volumes using a mathematical calculation to align into a common space. The volumes are warped to fit either the Talairach framework or the Montreal Neurologic Institute (MNI) framework, depending on the software program used.

Smoothing:

Images also undergo a selection of changes in preprocessing designed to filter out temporal variability not resulting from the task and high spatial frequency components that result in false positive detection of active voxels.

Temporal filtering allows the removal of specific frequencies within the data that may be due to confounding factors and create noise in the data. For instance, removal of high frequency components of the signal can remove the contribution of some physiological artifacts and removal of low frequency components can remove noise resulting from slow scanner drift (changes in voxel intensity) throughout the experiment.

Spatial filtering or smoothing reduces the detection of false positives by spreading the activation at each voxel across the neighboring voxels. This is accomplished by applying a Gasussian filter between 6-10mm full width half maximum (FWHM), which essentially averages the activation at each voxel with 2-3 nearby voxels.

Completion of preprocessing steps ensures that the data meet the assumptions necessary for statistical analysis which follows.

Statistical Analysis

Testing the hypothesis that some areas are significantly activated by the task being performed requires statistical testing to evaluate if the differences between the signal in the *active* condition and the signal in the *control* condition are more likely or less likely due to chance. If there is a low probability that the findings are due to chance, then we can conclude that the signal in these areas represents brain activation due to the task. In fMRI, this decision is accomplished by applying a statistical threshold where voxels whose probability exceed the threshold are labeled as non-significant and those that fall under the threshold are labeled as significant.

At a voxel level, the evaluation of this statistical probability is done through a t-test comparing the mean signal in the *active* condition to the mean signal in the *control* condition. The t-test takes into account the mean signal *between* the two conditions as well as the variability *within* each condition. If the effect size is large between groups and the individual variability within groups is small, the t-statistic will be higher, and will result in a conversion to a lower probability that the difference is due to chance.

$$t = \frac{\bar{x} - \bar{y}}{\surd(\sigma_x + \sigma_y)}$$

Equation A: Where means of x and y are divided by the standard deviation (σ) of x and y squared.

At the whole brain analysis level, the evaluation of statistical significance can be accomplished by applying a general linear model function. The general linear model (GLM) compares the observed data to a set of model factors (including the study design and any confounding factors) which may have influenced the experimental data. Using the GLM framework the total variability in the observed data is compared to the variability explained by the model and a probability map is created which represents the voxels whose activity is and is not sufficiently explained by the model, based on a threshold cut-off. See Figure 1.4 and Figure 1.5 for principles of GLM in fMRI and a summary of fMRI statistical analysis process.

Multiple comparisons

The main concern in fMRI data analysis is the problem of multiple comparisons. If one obtains even 10,000 voxels of data, this means that you are completing thousands of statistical tests. Without any correction, probability laws state that a portion of the statistical positive results will be due to chance. Depending on the threshold used, comparisons of 10,000 voxels can result in anywhere from hundreds to thousands of false positives. However, if a standard Bonferroni correction was applied to reduce the probability value for significance, then this would result in an excessively conservative threshold ($p < 0.000001$, in many cases).

Therefore, there is a delicate balance in setting the statistical threshold, and the decision to use a corrected threshold value (in between uncorrected and Bonferroni correction) must be weighed in each experimental task. Tasks with high amplitudes of activation may benefit from a reduction in false positives gained by correction, but tasks which result in more discrete activation patterns may not be able to hold up any significance under very conservative thresholds because of high levels of false negatives. This balance should be taken into consideration when designing the experiment.

Figure 1.4: General Linear Model (GLM) in fMRI

This figure is adapted from Huetel et al., 2004. Where analysis by the GLM finds the β values for each voxel representing how well a particular model (G) explains the data collected (X), with some undetermined error (ε).

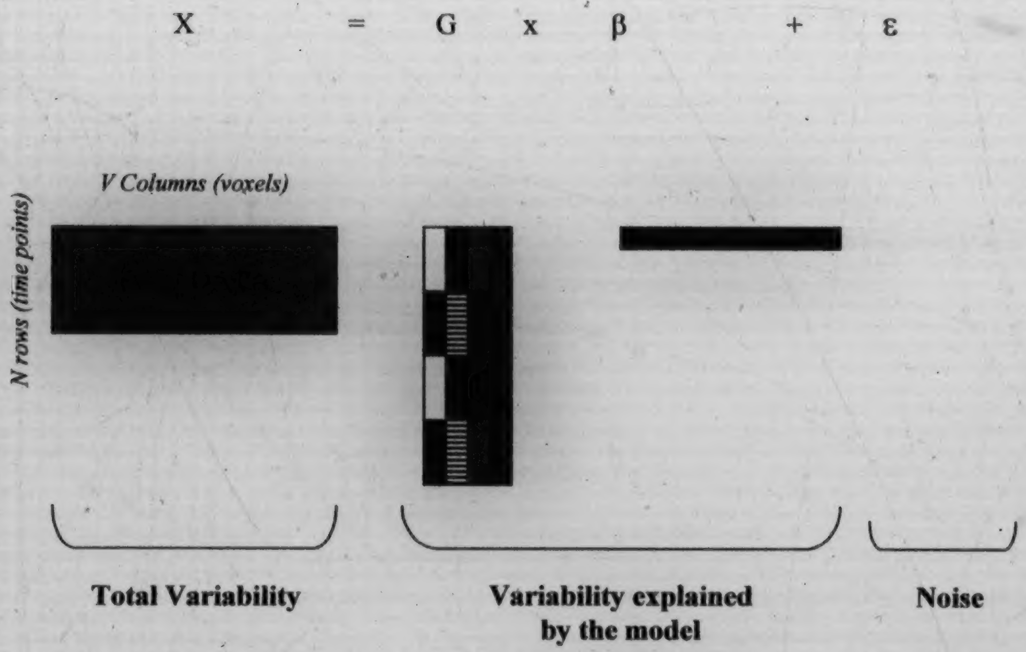
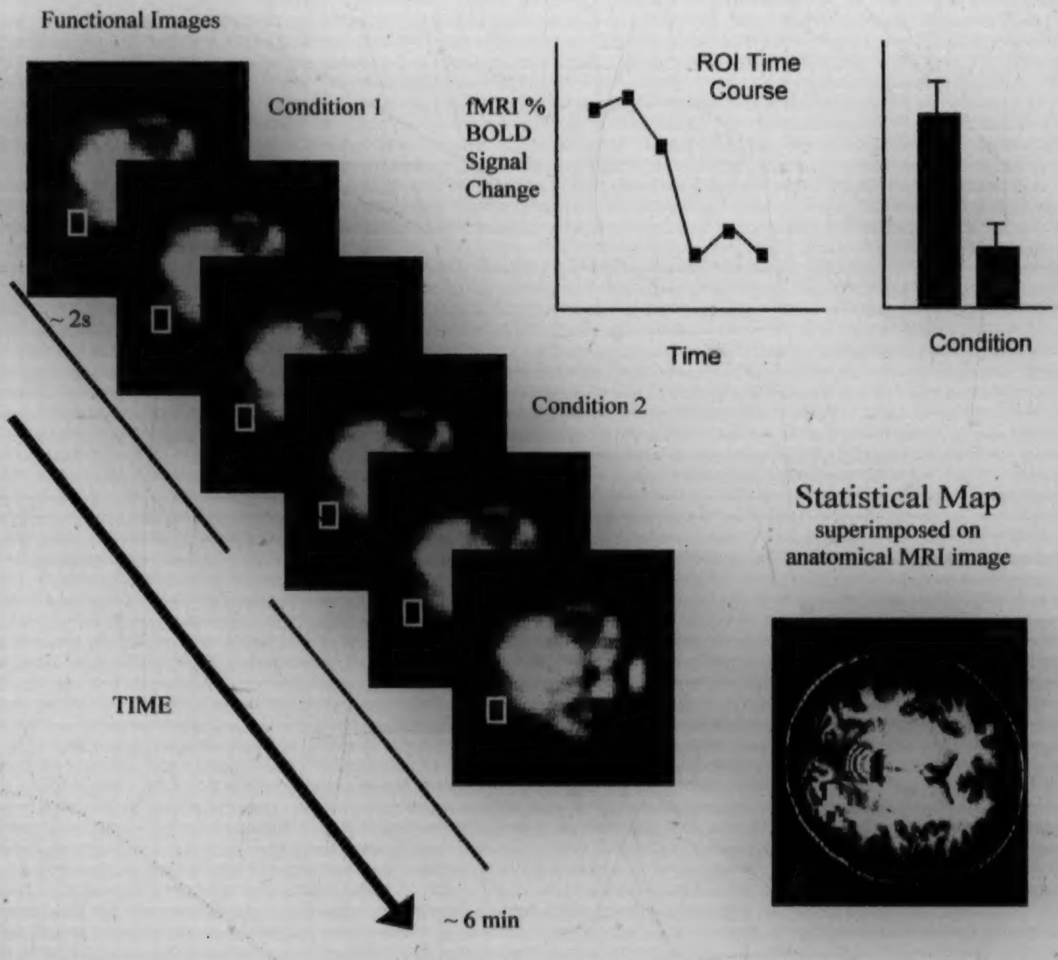

X = G x β + ε
V Columns (voxels)
N rows (time points)
Total Variability
Variability explained by the model
Noise

Figure 1.5: Statistical analysis of fMRI data.

This figure is adapted from fMRI for newbies by Jody Culham . It details the process of statistical analysis for one region of interest (yellow square) from the acquisition of images to the presentation of results. (http://psychology.uwo.ca/culhamlab/Jody_web/fmri4newbies.htm, 2007).


Functional Images
Condition 1
fMRI % BOLD Signal Change
ROI Time Course
Time
Condition
~ 2s
Condition 2
Statistical Map
superimposed on anatomical MRI image
TIME
~ 6 min

(Parts of this chapter have been published in Silverstone and Silverstone (2004) and Silverstone et al., (2005))

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Chapter 2. Thesis hypotheses and course of investigation

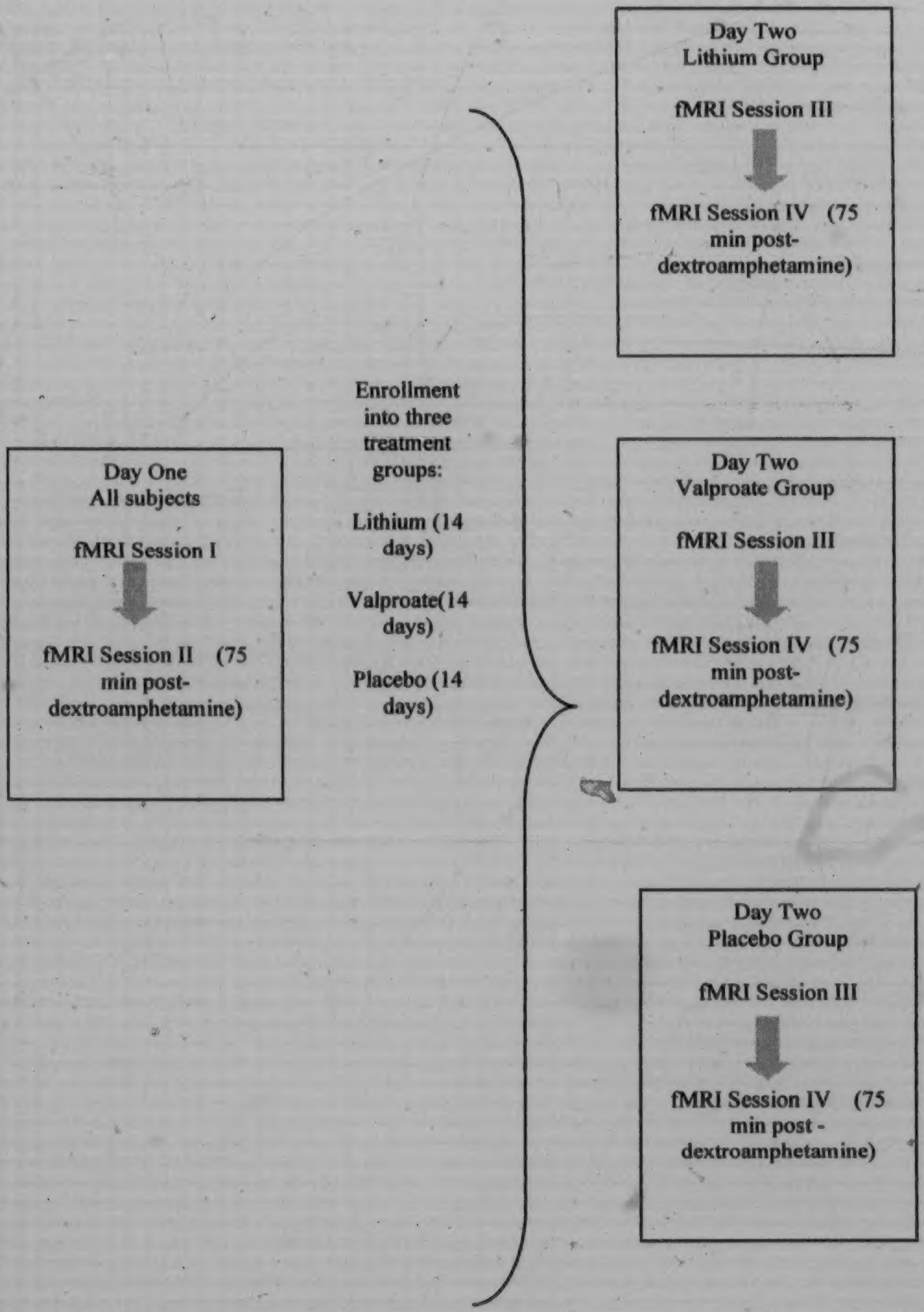
As described in the introductory chapter, there are evidently some differences in brain function (activity and cognition) in mood disorder patients compared to HCs and additional differences between unipolar and bipolar illness. However, there are still few consistent findings across studies of functional neuroimaging, and the extent to which these patient groups vary in brain function from each other is still largely unclear.

SECTION I

2.1 Investigations in HCs

Our initial investigations using fMRI in psychiatry were conducted in HC populations. Using HCs, it was primarily our goal to conduct some of the first functional imaging studies using fMRI at the University of Alberta, without the inherent difficulties that come from using a patient population. Using HCs meant that we were able to test out the entire fMRI system, as well as engage in development of data analysis techniques without worrying that pathophysiology or performance difficulties were impacting the data. See Figure 2.1 for the design of these investigations.

Figure 2.1: Study Design- Investigations in HCs using fMRI.


Day One
All subjects
fMRI Session I
fMRI Session II (75 min post-dextroamphetamine)
Enrollment into three treatment groups:
Lithium (14 days)
Valproate(14 days)
Placebo (14 days)
Day Two
Lithium Group
fMRI Session III
fMRI Session IV (75 min post-dextroamphetamine)
Day Two
Valproate Group
fMRI Session III
fMRI Session IV (75 min post-dextroamphetamine)
Day Two
Placebo Group
fMRI Session III
fMRI Session IV (75 min post - dextroamphetamine)

2.1.1 Dextroamphetamine effects on regional brain activity in HCs

Hypothesis: There will be a change in brain activation, compared to baseline, with the addition of dextroamphetamine in HCs, where dextroamphetamine is being used as a model for mania.

The functional imaging literature in manic bipolar patients is difficult to interpret; patients who are in an acute manic state are often on medications and our experience shows that valid data acquisition, inability to lie still and performance of the tasks in these patients is also a challenge. From previous experience, we had found it to be nearly impossible to scan manic patients, because they generally display poor attention to the task instructions and fail to complete the required tasks. For this reason, our first study in HCs was an investigation of the effects of dextroamphetamine on brain activity. Previously, Jacobs and Silverstone (1986) have suggested that dextroamphetamine serves as a model for mania, as healthy controls demonstrate a number of physiological and subjective effects similar to those observed in manic patients. In this case, our investigation sought to identify the specific cognitive domains (psychomotor speed, attention, working memory and verbal fluency) and areas of the brain in which brain activity changed significantly from baseline (fMRI Session I) with the administration of dextroamphetamine (fMRI Session II).

2.1.2 Effects of lithium and valproate on regional brain activity in HCs

Hypothesis: Lithium and valproate, two commonly prescribed mood stabilizers will normalize functional brain changes, physiologic and behavioral changes due to dextroamphetamine administration in HCs.

Lithium and valproate are two commonly prescribed mood stabilizer drugs. Both drugs are also first line therapy in the treatment of acute mania (Yatham et al., 2007). However, while sharing a common purpose in the treatment of BP, these are quite different drugs; lithium is a salt and valproate is an anticonvulasant. To investigate the effects of these drugs in our model of mania, subjects were randomized to three groups where they received treatment with 14 days of lithium, valproate or placebo. At the end of this treatment period subjects underwent two more scans to determine the effects of medication pretreatment on dextroamphetamine-induced brain changes in cognitive tasks (fMRI Session IV- fMRI Session III). Additionally, we were able to measure physiological (heart rate, blood pressure) and behavioral effects of dextroamphetamine after pretreatment with lithium and valproate.

Hypothesis: Treatment with lithium and valproate in HCs will not alter functional brain activity from baseline.

Our study design permitted one last important comparison regarding medication effects to be made in HCs. As previously stated, drawing conclusions in patient studies in BP (as well as other patient populations) is complicated by the fact that patients are often medicated, potentially with different combinations and types of drugs. However, there has been little exploration or attention given to the direct medication effects that mood stabilizers may exert in functional imaging results. This part of our investigations looked at the effects of 14 days of treatment with lithium and valproate on brain activity in healthy subjects (fMRI Session III- fMRI Session I). This was the first study to assess the medication effects of mood stabilizers on regional brain activity in healthy subjects.

SECTION II

2.2 Investigation of the gender effect in HCs

Hypothesis: Female and male HCs will not show differences in brain activation when tested on a variety of cognitive tasks.

During our studies in HCs, we contemplated the importance of additional factors that may play a role in modulating brain activity in our future patient studies. This led to a comparison of regional brain activity in our battery of cognitive tasks at baseline (fMRI

Session I) between males and females. We had felt that if gender was a significantly great modulator of regional brain changes then we would later on be compelled to separate patient groups based on gender. Additionally, this allowed us to compare the impact of task performance (a potential problem in impaired patient samples) and brain activation.

SECTION III

2.3 Investigation of executive function in mood disorders

The final studies that were undertaken were patient studies investigating regional brain activity changes in bipolar depression and MDD. See Figure 2.2 for a depiction of the study design.

2.3.1 Executive function in MDD vs. HCs

Hypothesis: MDD patients will demonstrate a decrease in dorsal prefrontal brain activation, compared to HCs on tests of executive function.

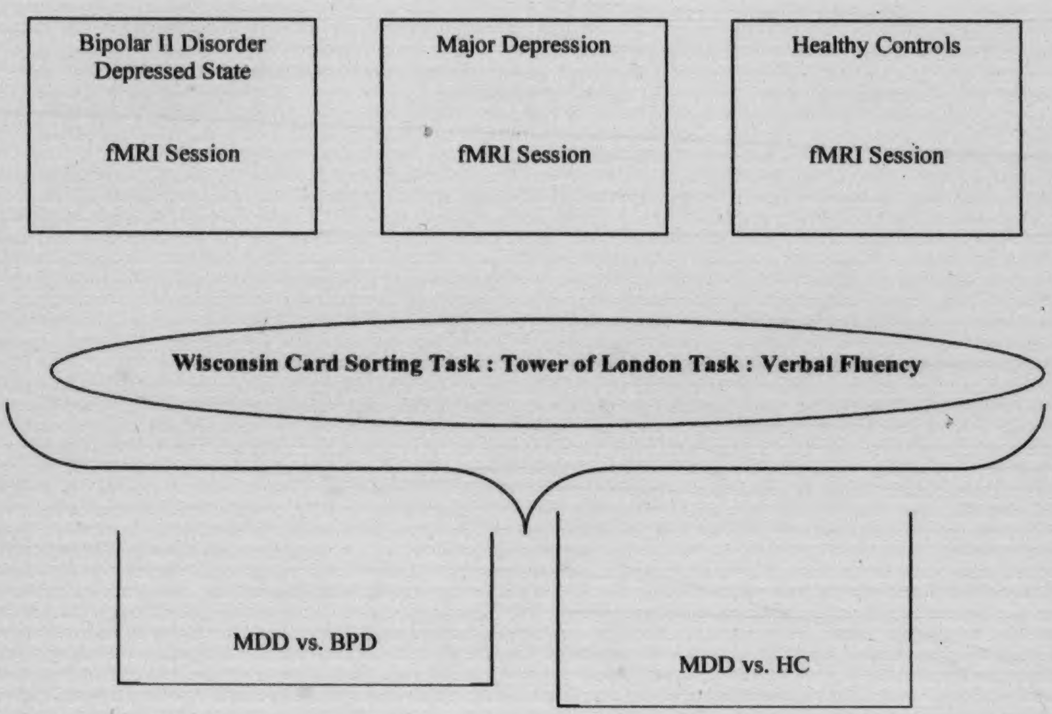
As a review of the literature shows, executive function deficits are characteristic in both BP and MDD. In MDD, there are consistent neuroimaging findings of decreased dorsal frontal lobe activity at rest and during cognitive acvitity, compared to HCs. Our study was designed to assess prefrontal cortex function in MDD patients during the performance of three executive function tasks, which would activate the prefrontal regions. The study is unique in that most fMRI studies do not assess brain activity across a range of tasks which is consistently how function is assessed behaviorally in cognitive test batteries. Therefore by examining brain activation in the TOL task, the WCST and a verbal fluency task, we have designed a novel study to assess prefrontal cortex function in MDD.

2.3.2 Executive function in MDD vs. BP depression

Hypothesis: Depressed BP II patients will demonstrate a decrease in dorsal prefrontal brain activation, compared to MDD patients, on tests of executive function.

The behavioral data show that bipolar depressed patients are more impaired that unipolar depressed patients in executive function, or frontal lobe tasks. Our objective was to make a comparison of prefrontal lobe brain activity in bipolar II depressed patients and major depression patients by imaging during the performance of three executive function tasks. While there appear to be some similarities between bipolar II depressed patients and MDD patients, there has been a very limited examination of differences between these groups in functional neuroimaging challenges. Based on behavioral findings of increased deficit in depressed bipolar patients (although not necessarily bipolar II patients), we proposed that patients with BP would show a greater decrease in activity in the prefrontal cortex than those patients with major depression, and that this trait-difference differentiates the two disorders.

Figure 2.2: Study Design - Investigations of executive function in mood disorders.


Bipolar II Disorder Depressed State
fMRI Session
Major Depression
fMRI Session
Healthy Controls
fMRI Session
Wisconsin Card Sorting Task : Tower of London Task : Verbal Fluency
MDD vs. BPD
MDD vs. HC

2.4 Bibliogaphy

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SECTION I

Chapter 3. Dextroamphetamine causes a change in human neural activity in vivo during cognitive tasks: An fMRI study utilizing BOLD

3.1 Introduction

Dextroamphetamine administration in healthy volunteers causes a range of cognitive and physiological changes, which include increased mood, alertness, energy, restlessness, mental speed, a decreased need for sleep, lowered appetite, and increased heart rate and blood pressure (Jacobs and Silverstone, 1986; Diehl and Gershon, 1992; Asghar et al, 2003). These effects may be mediated via an increase in extracellular concentrations of dopamine and noradrenaline, and, to a lesser extent of serotonin and glutamate (Hoebel et al 1989; Karler et al 1994; Kuczenski and Segal 1997; Reid et al 1997; Seiden et al 1993). The subjective effects of dextroamphetamine are clearly dose-dependent. While a 10 mg dose has been shown to cause an increase in subjective measures of arousal and mood, the difference between treatment with placebo and a 20 mg dose of dextroamphetamine is more robust (Silverstone et al., 1983). Dextroamphetamine acts principally to increase the concentration of catecholamines in the synaptic cleft (Masand and Tesar 1996).

In keeping with this, dextroamphetamine has also been suggested to change human CBF in areas innervated by dopamine pathways (Devous et al., 2001). Positron emmision tomography (PET) studies in primates using binding with [^{11}C]raclopride, a specific dopamine D_2/D_3 receptor antagonist, suggested that dextroamphetamine administration may alter activity in the dopaminergic mesocorticolimbic circuit (Drevets et al., 1999). Subsequent human *in vivo* studies (Drevets, 2001) also demonstrated a significant dopamine release in the ventral striatum following dextroamphetamine administration. Furthermore, the authors found that the change in $[^{11}C]$raclopride binding was inversely correlated with the change in subjective euphoria. Thus, there is evidence implicating the ventral striatum as an area of increased dopamine release by dextroamphetamine.

The dopamine system may play a role in coordinating cognitive function through the integration and adaptation of motor and limbic responses, likely through its influence upon working memory, attention and more executive functions, processes in which the prefrontal cortex is largely involved (Nieoullon, 2002). Given these findings, it would be likely that activation in these regions would be altered if dextroamphetamine were significantly affecting the dopaminergic system.

Despite the clear recognition of its cognitive and physiological effects, the actions of dextroamphetamine on regional brain activity remain uncertain. Neuroimaging studies in humans using PET and SPECT have resulted in mixed findings concerning the effects of dextroamphetamine on cerebral glucose metabolism (CGM) and CBF. Studies have found significant decreases (Wolkin et al. 1987), non-significant changes but a trend toward decreased CBF and CGM (Mathew and Wilson, 1985; Kahn et al. 1989), and both increases and decreases in CGM and CBF in areas innervated by dopamine pathways (Devous et al. 2001). An increase in global CGM has also been reported, but only with very high doses of dextroamphetamine (1mg/kg) (Vollenweider et al. 1998). Functional magnetic resonance imaging studies evaluating the effects of dextroamphetamine have also been inconclusive. Using fMRI, it has been found that dextroamphetamine administration can result in a reduction in the extent of sensory-induced activation (Howard et al. 1996) or an increase in the number of activated pixels (Uftring et al. 2001). In a group analysis, dextroamphetamine increased the BOLD signal during a task with increasing working memory (Mattay et al. 2000). However, in this study the effect of dextroamphetamine on performance and on signal change varied across individuals. Dextroamphetamine improved performance only in those subjects who had relatively low working memory capacity at baseline, whereas in the subjects who had high working memory capacity at baseline, it worsened performance. In subjects whose performance deteriorated, signal change was greater than that in subjects who had an improvement in performance. Similarly, Teicher and colleagues (2000) observed that administration of methylphenidate, a psychostimulant which inhibits dopamine reuptake, in children with ADHD resulted in a differential MRI response in the putamen in children who were hyperactive, compared to those who had normal levels of activity while unmedicated. This finding has been replicated in the cerebral vermis in boys suffering from ADHD (Anderson et al., 2002). Moreover, methylphenidate administration in children with ADHD has been shown to cause an oppositional effect on the BOLD response in the striatum, compared to healthy control children performing a cognitive test of inhibitory control (Vaidya et al., 1998). Another study has shown a differential response on a working memory task in individuals possessing different genotypes (Mattay et al., 2003). These studies demonstrate that the behavioral and neurophysiologic effects of dextroamphetamine are not homogeneous across individuals and that behavioral performance at baseline may influence the dose-response curve after psychostimulant administration.

Dextroamphetamine administration to healthy volunteers has also been used as a model for mania (Jacobs and Silverstone 1986). The subjective and behavioral effects of this drug closely mimic the behavioral and subjective reports of manic patients (Ashgar et al., 2003). In this regard, an investigation of the neurocircuitry changes during cognitive task performance in healthy controls treated with dextroamphetamine may additionally contribute to our understanding of dysregulations in the manic phase of bipolar disorder. The aim of the present study, therefore, was to use fMRI to determine the effect of dextroamphetamine on regional brain activation in healthy volunteers during a range of cognitive and motor tasks. To more accurately determine an effect, the change in both the number of pixels and the percent BOLD response were measured in all the tasks, pre- and post- dextroamphetamine. We examined a range of tasks which have been utilized previously in healthy controls and in various patient populations; these were tasks that we anticipated would activate the multiple brain regions of interest. Previous studies have previously demonstrated changes in regional brain activation during the performance of motor skills (Schroder et al 1995), verbal fluency tasks (Curtis et al 1998; Frith et al 1995; Yurgelun-Todd et al 1996), and working memory paradigms (Manoach et al 1999; Manoach et al 2000). We also utilized a reaction time test we had previously used to evaluate the effects of dextroamphetamine on vigilance and attention (Asghar et al 2003), and adapted this for use in an MRI environment. Our study encompasses an exploration of brain activity following dextroamphetamine administration in a variety of cognitive domains (attention, working memory, verbal fluency and motor behavior). In this regard, we believe the study significantly contributes to the past literature and will help identify task- and region- related effects of dextroamphetamine on regional brain activation during cognition.

3.2 Methods

3.2.1 Subjects and Study Design

The ethics committee at the University of Alberta gave ethics approval for the study and all participants gave full informed consent. Eighteen right-handed healthy volunteers were recruited from the university community through poster advertising to participate in the research study.

Using a semi-structured interview schedule, participants were screened for past or present history of psychiatric illness as well as history of psychiatric illness in their immediate family. Any history of this led to exclusion. Past medical history and abuse of alcohol, nicotine, caffeine or drugs were also determined, and subjects were excluded based on current abuse of these substances. Subjects who used any recreational drugs in the past six months (one year for stimulants such as amphetamine) were also excluded. At screening, a full medical history was obtained from all subjects and a medical examination was performed.

Subjects were required to fast from midnight the day prior to testing and were allowed only water during each session. An MRI safety screen was also performed to ensure safety in undergoing the MRI procedure.

An open label study design was used. Subjects received two fMRI examinations. During the first fMRI session, which lasted approximately forty-five minutes, subjects performed four types of tasks (described in detail in the following section): a motor task, a verbal task, a working memory task, and a reaction time task. Upon completion of the first fMRI session, subjects were administered a single oral dose of 25 mg dextroamphetamine and allowed to rest for 60 minutes. This timing was chosen to match the peak subjective response to dextroamphetamine (Silverstone et al 1998, 2002) which occurs 60 – 120 minutes after administration. The second fMRI scan was carried out immediately after the rest period.

3.2.2. Tasks

Motor Task

The motor task involved rapidly tapping the index finger. Subjects were instructed to "tap the index finger of the (given hand) as fast as you can comfortably while maintaining a steady pace". Instructions for the "Rest" and "Tapping" condition were given by a visual signal. Each condition (Rest or Tapping) was performed in four alternating blocks each lasting forty seconds. This experiment was done twice, once with the left hand and then again with the right hand.

Verbal Task

The verbal task utilized a word generation paradigm in which there were two conditions. In the first condition subjects were asked to repeat the word 'REST' silently until another instruction was given. In the second condition a series of ten single letters randomly chosen from the alphabet were displayed at four second intervals. During the display of a single letter, subjects responded by thinking of as many words as possible that begin with that letter and repeating them silently until another letter is presented or the 'REST' instruction appears. The experiment consisted of five forty-second blocks of each condition beginning with 'REST'.

Working Memory Task

The working memory task consisted of two conditions. In the first condition there was a series of ten arrows pointing to the left or to the right. Subjects responded by pressing the left or right button. In the second condition a five digit number was displayed for four seconds with the instruction 'Remember this Number'. Immediately after, a series of ten random single digits was presented. Subjects were asked to respond by pressing one button for yes and one for no if the single digit was or was not in the memorized number. In all, each condition was presented seven times in twenty-four second blocks pseudo-randomly arranged.

Reaction Time Task

For this task, subjects were asked to respond as quickly as possible to a certain criteria. First, a black cross appeared on the screen. Soon after, the black cross would appear with the target (a black square). Whenever the black cross and square appeared together subjects responded by pressing the button in their dominant hand as fast as possible. The delay between the appearance of the cross and the target was varied randomly from 300 – 1100 ms. Approximately 10% of the trials were actually catch trials designed to ensure subjects were engaged in the task. In a catch trial another black cross appeared instead of the target and subjects were instructed not to respond. Any responses to catch trials were considered errors, and the error rate could therefore be measured. In this experiment two conditions of the reaction task were alternated to maintain spatial attention (Beauchamp et al 2001; Cabeza and Kingstone 2001). In the first condition the cross and square appeared in the same location (attended location), and in the second condition the target appeared a distance away from the cross (unattended). There is significant evidence to suggest that spatial attention, such is needed to do this task, is analogous to a mental spotlight that requires a certain connectivity to operate properly. This task was performed in ten alternating blocks of each condition, twenty-four seconds in duration each.

3.2.3 fMRI Image Acquisition

The fMRI study was performed on a 1.5T Siemens Sonata scanner using a single shot EPI gradient echo sequence (Motor Tasks TR = 5040ms, TE = 50ms, 1.7x1.7mm, 3mm thick. Memory, Reaction, and Verbal Tasks TR = 4010ms, TE = 50ms, 1.7x1.7mm, 4mm thick) to acquire 30 contiguous slices obtained at an oblique angle along the anterior commisure-posterior commisure (AC-PC) line. A high resolution T1 weighted MPRAGE sequence was also acquired during the imaging session to overlay the functional analysis.

3.2.4 fMRI Data Analysis

Pre-processing and analysis were performed using Statistical Parametric Mapping (SPM), 1999 version (SPM99 - Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during pre-processing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. Sessions with realignment parameters of greater than 4 mm in the direction of translation (along the x,y,z axes) were excluded from the final statistical analysis, as were sessions with motion greater than 0.05 radians in a rotational plane (pitch, roll, yaw). The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 x 8 x 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2* weighted EPI functional images. After normalization, all volumes were resampled to 2 x 2 x 2 mm voxels using trilinear interpolation in space. Finally, all functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between-subject variability and to allow Gaussian random field theory to give corrected statistical inferences (Friston et al 1994).

Initial analysis was performed separately for each subject for each task. The model specified for each task was kept identical for all subjects and sessions to create identical design matrices. As part of this analysis three more pre-processing steps were performed using SPM99. First the data were high pass filtered to remove low-frequency drifts in the signal. In addition, the data were low pass filtered using the hemodynamic response function to remove high frequency noise. Effects due to global intensity fluctuations were removed when the data were proportionally scaled to a global mean of 100. The time series for each data set was analyzed according to the general linear model. A p-value threshold of 0.05 corrected for multiple comparisons was applied to obtain results.

Group analysis was performed by constructing a fixed effects model for each task. All sessions for all subjects were included in this model to generate a group average activation map. The coordinates of the most significantly active voxels in the group results were then used to create regions of interest (ROIs) for each task. ROI images were constructed using the automated anatomical labelling (AAL) template (Tzourio-Mazoyer et al. 2002), available for use with MRIcro software (Rorden and Brett, 2000).

For each subject the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels. From these activation maps a small volume correction (SVC) in SPM99 was applied to compute the activation within each ROI. We have used a SVC because we previously defined ROIs (areas of expected activation) in the statistical parametric map, based on the results of the multi-subject fixed effects analysis. To correct for multiple comparisons across the image is too conservative an estimate. Therefore, by applying a SVC the results allow the choice of appropriate thresholds given that our investigation is confined to ROIs of defined size and shape. We have used a corrected p-value threshold of 0.05 in the evaluation of the number of activated pixels in each ROI. The number of activated pixels in each ROI for a particular task was simply counted for each ROI and then analyzed using a conventional statistical program (Analyze It: Leeds, England), performing paired t-tests for within-group measures.

The BOLD signal intensity change was also calculated based on ROIs. The response was calculated using the MARSBAR toolbox for SPM (Brett et al 2002) over a seven-voxel sphere centered on the most significantly active voxel in each ROI. The number of voxels over which the fitted response was calculated was kept small in order to minimize averaging over non-significant voxels or large veins (Mulderink et al 2002). The quantity used in the subsequent statistical calculations for BOLD signal intensity was the average response calculated from the plateau portion of the hemodynamic response (eight seconds after stimulus origination until stimulus termination). Analysis was then performed using standard t-tests (Analyze It: Leeds, England) in the same fashion as was done in the analysis of the number of activated pixels for each ROI.

3.2.5 Response Data

Response and accuracy data were collected for the motor task, memory task, and reaction time task. Due to the nature of the word generation task no quantitative measures of performance could be obtained. For the motor task, the number of button presses was recorded during each forty-second epoch and averaged for that session. Standard t-tests were used to evaluate any changes in tapping frequency, measured in Hz. Both accuracy and reaction time were collected for the memory task and reaction time task and analyzed using t-tests.

3.2.6 Physiologic Data

Resting heart rate and both systolic and diastolic blood pressure were also measured at baseline and at 75 and 120 minutes post-dextroamphetamine. The physiological data were analyzed using repeated measures analysis of variance (RM-ANOVA).

3.3 Results

Eighteen subjects (13 males, 5 females) completed the study. The mean age of participants (± S.D.) was 25.4 years (± 6.51), and their mean weight (± S.D.) was 77.9 kg (± 10.1). The mean dose of dextroamphetamine was thus 0.32 mg/kg.

3.3.1 Cognitive and Physiologic Measures

As anticipated, there was a statistically significant dextroamphetamine-induced increase in heart rate, systolic blood pressure, and diastolic blood pressures (Table 3.1).

Subject tapping frequency was significantly increased after administration of amphetamine for the left hand ($p < 0.05$), but not the right hand finger-tapping task ($p = 0.400$) (Table 3.2). For the reaction time task, reaction times were also significantly better after dextroamphetamine ($t = 6.80$, $p < 0.000$). However, there was no significant difference in the number of errors ($t = 1.77$, $p = 0.094$) (Table 3.3). Similarly, subjects performing the working memory task responded faster to all three conditions after dextroamphetamine (Control $t = 2.85$, $p= 0.008$, 5 Digit Memory $t = 2.34$, $p= 0.0253$, 2

Digit Memory t = 3.80, p = 0.0006) (Table 3.4). The administration of dextroamphetamine had no effect on the number of errors incurred during the memory task (t = 1.09, p = 0.283).

Table 3.1: The effects of dextroamphetamine on heart rate and blood pressure.

Measurements were taken at baseline, 75 minutes after dextroamphetamine (Pre fMRI), and at 120 minutes post-dextroamphetamine (Post fMRI). *Blood pressure, both systolic and diastolic, was significantly higher for baseline vs. pre-fMRI, and baseline vs. post-fMRI, $p \leq 0.05$. **Heart rate was significantly higher for baseline vs. post-fMRI, and pre-fMRI vs. post-fMRI, $p \leq 0.05$.

Mean Heart Rate (beats per minute ± SD)		
Baseline	(t = 0)	66.2 ± 6
Pre fMRI	(t = 75 min)	70.9 ± 8
Post fMRI	(t = 125 min)	79.3 ± 11
Mean Blood Pressure (mmHg ± SD)		
Systolic		
Baseline	(t = 0)	107.1 ± 12
Pre fMRI	(t = 75 min)	124.3 ± 14
Post fMRI	(t = 125 min)	122.9 ± 11
Diastolic		
Baseline	(t = 0)	78.1 ± 9
Pre fMRI	(t = 75 min)	84.1 ± 7
Post fMRI	(t = 125 min)	86.6 ± 5

Table 3.2: The effects of dextroamphetamine on rate of motor tapping.

Values represent mean ± S.E. of rate of finger tapping (Hz).

Motor Task	**Tapping Rate Pre - AMPH (Hz)**	**Tapping Rate Post – AMPH (Hz)**	**p-value**
Tapping Right Hand	3.36 ± 0.19	3.59 ± 0.20	0.129
Tapping Left Hand	2.91 ± 0.17	3.33 ± 0.17	< 0.05 *
p-value	**<0.05 ***	**<0.05 ***	-

Table 3.3: The effects of dextroamphetamine on reaction time and errors in the reaction task.

Values represent mean ± S.E. of rate of reaction (milliseconds) and mean number of errors ± S.E.

	Time to reaction for attended trial (msec)	**Time to reaction for unattended trial (msec)**	**Number of Errors**
Pre –d-AMPH	312.20 ± 9.3	332.67 ± 11.5	4.39 ± 0.9
Post- d-AMPH	281.24 ± 7.5	303.91 ± 9.7	3.22 ± 0.7
p-value	<0.0001*	< 0.0001*	0.094

Table 3.4: The effect of dextroamphetamine on reaction time and errors in the working memory task.

Values represent mean ± S.E. of rate of reaction (milliseconds) and mean number of errors ± S.E.

	Time to reaction for arrow condition (msec)	**Time to reaction for 5- digit memory condition (msec)**	**Number of Errors**
Pre – d-AMPH	481.45 ± 16.0	897.64 ± 33.2	3.94 ± 0.7
Post – d-AMPH	422.25 ± 13.0	797.71 ± 38.02	2.88 ± 0.7
p-value	0.008*	0.0258*	0.283

3.3.2 fMRI measurements

During the verbal task, in the pre-amphetamine session, activation was seen in the left and right frontal cortex as well as the anterior cingulate, and the left superior parietal lobule (Figure 3.1). The effects of dextroamphetamine were to significantly reduce, or show a trend towards reduction, in the number of activated pixels in the parietal lobule, pre-central and cingulate gyri, as well as the supplementary motor area (Table 3.5). Dextroamphetamine also significantly reduced the BOLD contrast in the parietal lobule (Table 3.6).

For the working memory task, activation prior to amphetamine administration occurred in the left and right insula, left and right superior parietal lobule and left frontal cortex (Figure 3.2). Dextroamphetamine significantly reduced the number of activated pixels in the left insula, and there were trends towards reductions in other regions (Table 3.5); dextroamphetamine also significantly reduced the BOLD response in the left dorsolateral prefrontal cortex and the cingulate gyrus.

In the first session prior to dextroamphetamine administration, activation was seen during the reaction time task in the occipital cortex (primary visual cortex), superior and inferior parietal lobule, and fusiform gyrus (Figure 3.3). Dextroamphetamine significantly decreased the number of activated pixels in the left lingual gyrus (Table 2) and significantly reduced the BOLD contrast in the right middle occipital gyrus and precuneus (Table 3.6).

During the motor task, activation (during the pre-dextroamphetamine session) occurred in the contralateral primary motor cortex, cingulate, and superior temporal regions (Figure 3.4). Dextroamphetamine had no statistically significant effects on the number of activated pixels, and, in contrast to previous tasks, significantly increased the BOLD contrast in the left inferior frontal gyrus during left hand motor activity (Table 3.6). However, there were no changes in BOLD contrast during right hand motor activity after dextroamphetamine administration.

Table 3.5: The effects of dextroamphetamine on the number of activated pixels for the verbal task, memory task, reaction task, motor left hand task, and motor right hand task (mean ± SE).

*Only areas that showed a significant change are shown. * indicates a significant difference of $p \leq 0.05$.*

Effects of Dextroamphetamine on the Number of Activated Pixels

Region of Interest	Pre Amphetamine	Post Amphetamine	p-value
Verbal Task			
Left Inferior Parietal Lobule	672 ± 169	302 ± 63	0.02*
Left Pre-Central Gyrus	824 ± 175	545 ± 119	0.05*
Memory Task			
Left Insula	35 ± 13	8 ± 4	0.05*
Reaction Task			
Left Lingual Gyrus	390 ± 137	677 ± 203	0.05*
Motor Right Hand, Motor Left Hand			
No significant changes			

Table 3.6: The effects of dextroamphetamine on the magnitude of BOLD contrast for the verbal task, memory task, reaction task, motor left hand task, and motor right hand task (mean ± SE).

Only areas that showed a significant change are shown. * indicates a significant difference of $p \leq 0.05$.

Effects of Dextroamphetamine on BOLD Contrast

Region of Interest	Pre Amphetamine	Post Amphetamine	p-value
Verbal Task			
Left Inferior Parietal Lobule	1.8 ± 0.12	1.6 ± 0.10	0.02*
Memory Task			
Left Dorsolateral Prefrontal Cortex	1.4 ± 0.11	1.2 ± 0.08	0.05*
Cingulate Gyrus	1.2 ± 0.09	1.0 ± 0.08	0.05*
Reaction Task			
Right Middle Occipital Gyrus	1.2 ± 0.12	0.9 ± 0.09	0.02*
Precuneus	1.5 ± 0.13	1.7 ± 0.16	0.03*
Motor Left Hand			
Left Inferior Frontal Gyrus	1.1 ± 0.11	1.8 ± 0.31	0.05*
Motor Right Hand			
No Significant Changes			

Figure 3.1: Brain activation in verbal task in healthy controls.

The fMRI group analysis of 18 subjects at baseline for the verbal task is shown. Activation can be seen in the left and right frontal cortex as well as anterior cingulate and left superior parietal lobule (Left of image =Left side of brain, Right of image=Right side of brain). Brighter intensity reflects higher statistical significance.

Figure 3.2: Brain activation in working memory task in healthy controls.

The fMRI group analysis of 18 subjects at baseline for the working memory task is shown. Activation can be seen in the left and right insula, left and right superior parietal lobule and left frontal cortex (Left side of image=Left side of brain, Right side of image=Right side of brain). Brighter intensity reflects higher statistical significance.

Figure 3.3: Brain activation in reaction time task in healthy controls.

The fMRI group analysis of 18 subjects at baseline for the reaction time task is shown. Activation can be seen in the occipital cortex (primary visual cortex), superior and inferior parietal lobule, and fusiform gyrus (Left side of image=Left side of brain, Right side of image=Right side of brain). Brighter intensity reflects higher statistical significance.

Figure 3.4: Brain activation in motor task in healthy controls.

The fMRI group analysis of 18 subjects at baseline for the motor task is shown for both the left (A) and right (B) motor cortex (Left side of image=Left side of brain, Right side of image=Right side of brain). Activation can be seen in the contralateral primary motor cortex, cingulate, and superior temporal regions. Brighter intensity reflects higher statistical significance.

A.

B.

3.4 Discussion

The effects of dextroamphetamine on pulse, blood pressure and reaction times are fully consistent with those from previous studies in healthy volunteers (Silverstone et al 1983; Dommisse et al 1984; Rapoport et al 1978; Hamilton et al 1983; Silverstone et al 1998). The major finding from this study was that following dextroamphetamine there was a significant decrease in regional brain activity measured by the BOLD response following cognitive, but not motor, tasks. These changes were most prominent during the verbal task and working memory tasks. In contrast, during the left motor task there was in increase in the BOLD contrast in one brain region. The changes we observed were region- and task- dependent.

The extent of brain activation was most altered in the verbal fluency task, while both the memory task and the reaction task showed greater alterations in the percent BOLD signal (magnitude of brain activation) due to dextroamphetamine. Previous evidence implicates the mesocorticolimbic system as a possible site of dextroamphetamine action (Drevets et al., 2001, 1999). Dextroamphetamine may affect multiple pathways linked to this system. In the present study, findings of altered activity during the working memory task in the frontal lobe, the cingulate and the insula correspond to dextroamphetamine acting in this pathway. However, those areas in which we observed a significantly decreased regional activation in the reaction task and in the verbal fluency task diverge from the mesocorticolimbic system. Altered activity in more posterior brain areas in the reaction task and parietal areas during the verbal fluency task are consistent with brain areas integrated in the performance of the tasks. Changes in the execution of these tasks (although we have no behavioral measures for the verbal fluency task) may be largely reflected by the alterations in regional brain activation in these areas.

Contrary to the decreased BOLD response that we observed during the performance of the cognitive tasks post-dextroamphetamine, we did observe an increase in BOLD signal in one brain area (left inferior frontal gyrus) during the left hand motor task, after dextroamphetamine was administered. We cannot clearly explain why a significant increase was observed in the left inferior frontal gyrus. However, an increase in percent BOLD signal change, although not significant, was also observed in this brain area in a study conducted by Uftring and colleagues (2001), using fMRI to investigate amphetamine's effect on regional brain activation during right hand finger tapping.

Our finding of reduced regional brain activation during cognitive task performance following dextroamphetamine is consistent with some previously published research. However, direct comparisons between studies examining CBF and the present study are somewhat difficult because changes in BOLD contrast do not necessarily correspond to changes in CBF. Unlike PET and SPECT, BOLD fMRI does not measure blood flow directly. The BOLD response measures changes in oxygen content in the blood, but because BOLD also depends on oxygenation levels, it is important to note that this is not the same as blood flow. The quantitative interpretation of the BOLD signal remains in doubt as the BOLD signal depends on oxygen extraction, not just blood flow. Nonethless, using PET and SPECT imaging techniques, dextroamphetamine has been shown to be a vasoconstrictive agent leading to decreases in global cerebral blood flow and metabolism

(Mathew and Wilson, 1985; Wolkin et al. 1987; Kahn et al. 1989). This effect also occurs with other psychostimulants such as caffeine (Mathew et al. 1983). However, not all studies concur with these findings. In a study evaluating the response to dextroamphetamine (0.4mg/kg) on resting CBF, it was concluded that it caused regional increases and decreases in specific cognitive areas, increasing regional CBF in two prefrontal regions, inferior frontal lobe, brain stem, temporal lobe and thalamus and decreasing regional CBF to motor cortex, visual cortex, fusiform gyrus and areas of the temporal lobe (Devous et al. 2001). Furthermore, in another study using two abstract reasoning tasks to evaluate the response to dextroamphetamine (0.25 mg/kg), the WCST and the Ravens Progressive Matrices Task (RPMT), blood flow increased in the inferior frontal gyrus during WCST but decreased during RPMT. In a similar manner, blood flow in the hippocampus decreased during WCST performance and increased during RPMT (Mattay, 1996). This suggests that amphetamine may not have consistent regional effects. Rather, a region-dependent, task-related effect is supported by findings from an fMRI study investigating a working memory task (Mattay et al. 2000). This group found that following dextroamphetamine there was an increase in the BOLD contrast in a high working memory load condition, whereas a decrease in the BOLD contrast was found during performance of a low working memory load condition.

Moreover, another study utilized fMRI to measure the BOLD contrast change and the number of activated pixels in regions of interest while performing either a tone decision task or a motor task (Uftring et al. 2001). This study found a significant increase in the number of activated pixels in the left and right primary auditory cortices for the tone decision task, and the ipsilateral primary sensorimotor cortex and right middle frontal area during the motor task. In this study it was found that there were no changes in the magnitude of the BOLD contrast caused by dextroamphetamine. Additional findings in schizophrenic patients, has shown that dextroamphetamine administration causes a global reduction in rCBF, although the authors state that this finding was nonsignificant (Daniel et al. 1991).

The motor task within this study is a control task. In the present study, the finger tapping task resulted in activation in motor areas, pre- and post- dextroamphetamine. This would suggest that the resulting BOLD effect observed post- dextroamphetamine is not altered due to overall neurovascular effects of the drug. This is similar to findings with methylphenidate (Rao et al., 2000). While the rate of finger tapping during the left hand motor task was increased following dextroamphetamine administration, we do not believe that this has negatively influenced the effectiveness of this motor task as a control. All subjects maintained an average rate of tapping between 2.91Hz – 3.59Hz. Previous studies by Rao and colleagues (1996, 2000) have suggested that an increase in rate of finger tapping from 2Hz to 5Hz results in a negligible effect upon the number of activated voxels. Contrary to the decreased BOLD response that we observed during the performance of the cognitive tasks post-dextroamphetamine, we did observe an increase in BOLD signal in one brain area (left inferior frontal gyrus) during the left hand motor task after dextroamphetamine was administered. We cannot clearly explain why a significant increase was observed in the left inferior frontal gyrus. However, an increase in percent BOLD signal change, although not significant, was also observed in this brain area in a study conducted by Uftring and colleagues (2001), using fMRI to investigate amphetamine's effect on regional brain activation during right hand finger tapping

Studies looking at the effects of other stimulants such as caffeine and cocaine have also shown that decreases in CBF can occur after drug administration (Mulderink et al. 2002; Gollub et al. 1998). Interestingly, the effects of the psychostimulant methylphenidate are to also reduce CBF and volume after treatment or to increase these parameters after cessation of the drug (Anderson et al 2002; Langleben et al 2002; Rao et al 2000; Teicher et al 2000). These two drugs can have similar subjective effects, and both increase functionally available brain dopamine (Elia et al 1990; Wilens and Spencer 2000), so it is of interest that both drugs have also been reported to reduce regional CBF. Previous studies have shown that baseline performance, particularly on working memory, may influence the behavioral response to stimulants (Anderson et al., 2002, Mattay et al., 2000, Teicher et al., 2000). Analysis of the baseline performance of the reaction task and the memory task in our study showed no impact upon our results.

In considering the results from this study, there are some limitations. While few women took part in this study, it is important to recognize the effect of gender and menstrual cycle on our results. In analysis of a gender effect upon the ROI activation, we observed a significantly decreased number of pixels activated in females in the supplementary motor cortex and the cingulate gyrus, during the verbal task, pre- and post-dextroamphetamine. The explanation of this gender effect seems unclear. However, menstrual cycle phase may have caused unforeseen changes in regional brain activation in our sample of women. In 2001, Dietrich and colleagues investigated word stem completion in women (at different times in their menstrual cycle) using fMRI. Their results suggest altered regional brain activation during this task in women during the high estrogen phase compared to during menses. Moreover, Justice and de Wit (1999) identified that menstrual cycle phase affects response to dextroamphetamine. Unfortunately, because we have not assessed menstrual cycle phase in the women it is impossible to say at which point in the cycle women were imaged and therefore we cannot rule out any effect of menstrual cycle on our results.

In addition, drug use was not determined by using a urine screen. Moreover, we have used an open-label design in this study to investigate the effects of dextroamphetamine on regional brain activation. Ideally, we would have included a placebo group. A future randomized trial with placebo and dextroamphetamine groups would be beneficial. An open label design could have caused some subjects to become biased in their subjective and behavioral responses to dextroamphetamine. Also, we acknowledge that we limit the interpretation of results obtained during the verbal task, as participants were unable to offer a behavioral response. In the future, a response technique would help assess behavioral changes in this task.

It would also have been useful to randomize the timing of dextroamphetamine administration between the first and second sessions. By not randomizing the order of sessions we may have allowed the effects of task-repetition to influence our results.

In conclusion, the results from the present study support previous suggestions that dextroamphetamine can reduce regional brain activity during a range of cognitive tasks. These effects may possibly be mediated by the actions of dextroamphetamine upon the dopaminergic system. The effects of dextroamphetamine appear to be both regio-n and task- specific.

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The findings of this study demonstrated that dextroamphetamine administration as a model for mania in healthy controls produces a decrease in brain activity during cognitive task completion, although this is a task- and regional- specific decrease in activity. This provides a framework of brain activation changes in a potential model for mania upon which to test the effects of two commonly prescribed mood stabilizers, lithium and valproate.

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Chapter 4. Lithium and valproate attenuate dextroamphetamine-induced changes in brain activation.

4.1 Introduction

It has previously been suggested that dextroamphetamine administration to healthy volunteers serves as a model for the mania experienced by patients suffering from BP (Jacobs and Silverstone, 1986), since its administration leads to a number of well documented physiologic and subjective effects similar to mania, including mood elevation and increased activity (Jacobs and Silverstone, 1986; Diehl and Gershon, 1992; Asghar et al., 2003). Recently we have also demonstrated that dextroamphetamine administration causes a decrease in regional brain activity during the performance of a battery of cognitive tasks in a variety of cognitive domains as measured by fMRI (Willson et al., 2004). Lithium and valproate are commonly used mood stabilizers for the treatment of bipolar disorder, and there is some evidence to suggest that the behavioral effects of dextroamphetamine may be attenuated by lithium (Flemenbaum, 1974; van Kammen and Murphy, 1975), although this finding has not been reproduced in all studies (Silverstone et al., 1998).

We have recently demonstrated that administration of dextroamphetamine causes a decrease in regional brain activation during the performance of several cognitive tasks (Willson et al., 2004). There is also evidence that dextro-amphetamine stimulates the PI-cycle (Yu et al., 2003, Silverstone et al., 2002; Barkai et al., 1981) and this may conceivably be the mechanism responsible for its effects on brain activation. There is also good evidence that both lithium and valproate can attenuate the PI-cycle, probably acting via different mechanisms (Gurvich & Klein, 2002). Therefore, to further examine this in the present double-blind, placebo-controlled study we have examined whether pre-treatment with either lithium or valproate attenuates the dextroamphetamine-induced changes in brain activation in HCs, as measured by fMRI.

4.2 Methods

This study was approved by the ethics board of the University of Alberta Hospital.

4.2.1 Subjects

Thirty-three right-handed healthy volunteers were recruited through poster advertising from the university community. Subjects underwent a medical exam and medical history, and a detailed semi-structured clinical interview (structured clinical interview for DSM-IV) to rule out past or present psychiatric illness. Past and present drug and alcohol use were assessed and subjects were excluded based on current abuse of these substances. Subjects who had used recreational drugs in the past six months or amphetamine in the past year were excluded from participating. At 12:00am before the day of the scan, subjects were required to fast until all scans were complete.

4.2.2 Study Design

A double blind study design was used. Subjects were randomized to receive capsules containing placebo (lactose powder), lithium (900mg daily), or sodium valproate (500mg for 3 days; 1000mg daily thereafter) for 14 days prior to scanning. Nine subjects received lithium, 12 received valproate, and 12 received placebo. On day 14, subjects underwent two fMRI examinations of the same duration (approx. 45 minutes) in which they performed a working memory task, a word generation paradigm and a spatial attention task. These tasks have been previously described in detail (Willson et al., 2004). Upon completion of the first scan, subjects were administered a single oral dose of dextroamphetamine (25mg). The second scan began 75 minutes later, which coincides with the peak subjective response to dextroamphetamine (Silverstone et al., 1998, 2002). Prior to scanning, a drug plasma level for those in treatment groups was obtained, which determined serum levels of lithium and valproate. Plasma valproate levels ranged between 0.52-0.88 mmol/L, and plasma lithium levels ranged between 0.39-0.77 mmol/L.

All imaging parameters and tasks were identical to those described previously (Willson et al., 2004). The three tasks measured were a working memory task (7 blocks each condition; block length 24.1sec) in which subjects had to memorize a number and respond yes or no if the memorized number was presented; a spatial attention task (10 blocks each condition; block length 24.1sec) in which subjects had to respond when a black square and/or cross appeared; and a word generation paradigm (5 blocks each condition; block length 40.1sec) in which subjects had to think of as many words beginning with a specific letter as possible. The fMRI images were collected on a 1.5T

Siemens Sonata scanner, using a single shot EPI gradient echo sequence (Memory, Reaction and Verbal Tasks TR = 4010ms, TE = 50ms, 1.7 x 1.7 mm, 4 mm thick) to acquire 30 contiguous slices obtained at an oblique angle along the AC-PC line. A high resolution T1 weighted MPRAGE sequence was also obtained for overlay of the functional analysis.

4.2.3 fMRI Data Analysis

Pre-processing and analysis were performed using Statistical Parametric Mapping (SPM), 1999 version (SPM99 - Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during pre-processing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation, and a mean image was created of the entire time series for each data set. Sessions with realignment parameters of greater than 4 mm in the direction of translation (along the x,y,z axes) were excluded from the final statistical analysis, as were sessions with motion greater than 0.05 radians in a rotational plane (pitch, roll, yaw). The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 x 8 x 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2* weighted EPI functional images. After normalization, all volumes were resampled to 2 x 2 x 2 mm voxels using trilinear interpolation in space. Finally, all functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between-subject variability and to allow Gaussian random field theory to give corrected statistical inferences (Friston et al 1994). Initial analysis was performed separately for each subject for each task. The model specified for each task was kept identical for all subjects and sessions to create identical design matrices. As part of this analysis three more pre-processing steps were performed using SPM99. First the data were high pass filtered to remove low-frequency drifts in the signal. In addition, the data were low pass filtered using the hemodynamic response function to remove high frequency noise. Effects due to global intensity fluctuations were removed when the data were proportionally scaled to a global mean of 100. The time series for each data set was analyzed according to the general linear model. A p-value threshold of 0.05 corrected for multiple comparisons was applied to obtain results. Previously, we have performed a group analysis on 18 volunteers (Willson et al., 2004) by constructing a fixed effects model for each task. ROIs for each task were then compiled using the most significantly activated voxels from the group average generation maps (Willson et al., 2004). ROI images were constructed using automated anatomical labeling (AAL) software (Tzourio-Mazoyer et al., 2002), running with MRIcro software (Rorden and Brett, 2000). We have assessed activation in these same ROIs in the present study.

For each subject the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels. From these activation maps a small volume correction (SVC) in SPM99 was applied to compute the activation within each ROI. We have used a SVC because we previously defined ROIs (areas of expected activation) in the statistical parametric map, based on the results of the multi-subject fixed effects analysis. To correct for multiple comparisons across the image is too conservative an estimate. Therefore, by applying a SVC the results allow the choice of appropriate thresholds given that our investigation is confined to ROIs of defined size and shape. We have used a corrected p-value threshold of 0.05 in the evaluation of the number of activated pixels in each ROI. The number of activated pixels in each ROI for a particular task was simply counted for each ROI. The BOLD signal intensity change was also calculated based on regions of interest. The response was calculated using the MARSBAR toolbox for SPM (Brett et al 2002) over a seven-voxel sphere centered on the most significantly active voxel in each ROI. The number of voxels over which the fitted response was calculated was kept small in order to minimize averaging over non-significant voxels or large veins (Mulderink et al 2002). The quantity used in the subsequent statistical calculations for BOLD signal intensity was the average response calculated from the plateau portion of the hemodynamic response (eight seconds after stimulus origination until stimulus termination. For both the number of activated pixels and the BOLD signal response, values obtained pre-dextroamphetamine administration were subtracted from values obtained post-dextroamphetamine administration. This resulted in values for the change in both the number of activated pixels and the change in the BOLD signal response due to dextroamphetamine administration in all subjects in the three treatment groups for each task.

A one-way analysis of variance (ANOVA) was used to assess the treatment effect across groups in each task, and the size and magnitude of the BOLD response. *Post hoc* analyses to correct for multiple comparisons were performed. If significant differences were identified, an independent Student's *t*-test was used to test for significant differences ($p \leq 0.05$) in the mean total number of activated pixels and BOLD signal between groups, over the regions of interest in each task. *Post hoc* independent Student's *t*-tests were also conducted to assess significant differences in a separate analysis between the groups of each ROI in each task (if significant in the ANOVA). Independent t-tests also identified significant differences in groups in measures of age and weight. All results are shown as the mean ± SEM.

4.3 Results

All 33 subjects completed the study (23 males, 10 females). Twelve subjects (7 males, 5 females) received treatment with placebo (mean age 25.8 ± 1.7 years; mean weight 160.8 ± 8.8 lbs), 12 subjects (10 males, 2 females) received treatment with valproate (mean age 27.1 ± 1.8 years; mean weight 166.7 ± 7.6 lbs), 9 subjects (6 males, 3 females) received treatment with lithium (mean age 25.8 ± 2.9 years ; mean weight: 169.4 ± 7.6 lbs). There were no significant differences between these groups in terms of age or weight. Two subjects (one placebo, one valproate) did not complete both a pre- and post-dextroamphetamine scan due to technical difficulties. Therefore these subjects have been excluded from the analyses as we could not assess the change due to dextroamphetamine in these volunteers.

4.3.1 fMRI measurements

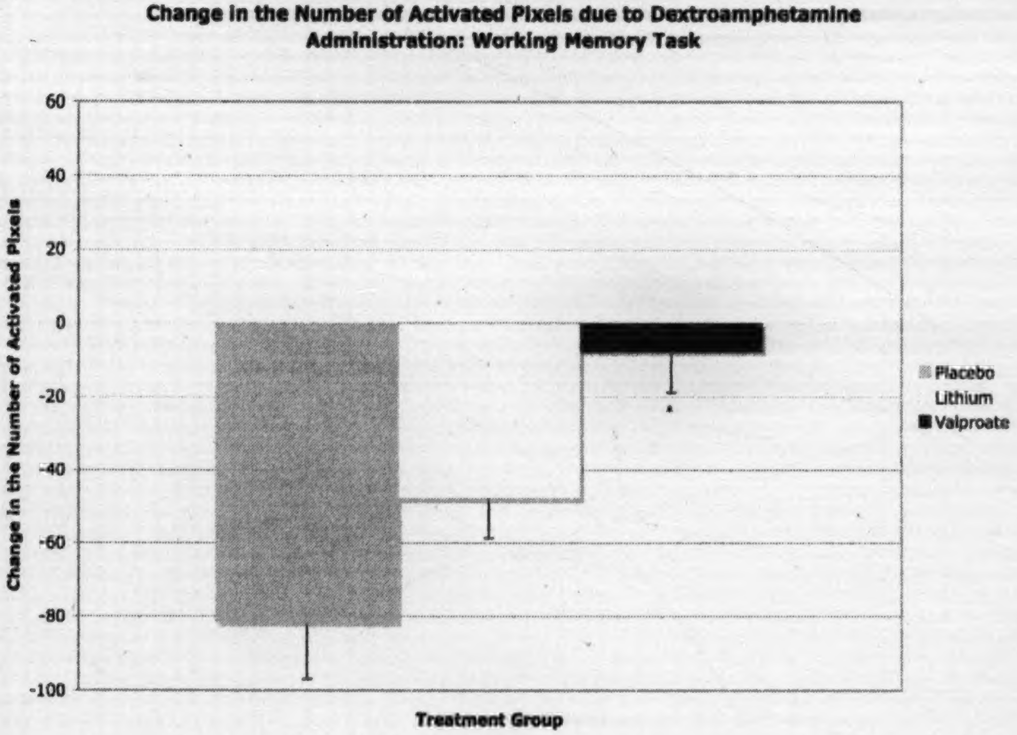
Working Memory Task:

There was a treatment effect observed for the change in the number of activated pixels ($df = 2$, $F = 8.99$, $p < 0.001$) (Figure 4.1). *Post hoc* analysis using the Tamhane correction for multiple comparisons revealed a significant difference between the placebo and valproate groups (p< 0.000). A significant increase in the mean change in the number of activated pixels due to dextroamphetamine administration was observed in the valproate group, compared to the placebo group (placebo = -81.95 ± 15.1; valproate = -7.88 ± 11.0; p < 0.001). *Post-hoc* analysis of nineteen regions of interest showed a trend to significant difference between the valproate and placebo treated groups in the right insula (Table 4.1).

No significant treatment effect was observed between the groups in measures of mean BOLD signal change (df = 2, F = 2.55, p = 0.08), therefore no *post hoc* ROI analysis was performed.

Figure 4.1: Graph showing the mean change (± S.E. error bars) in the number of activated pixels due to dextroamphetamine administration for each treatment group (placebo, lithium, valproate) during performance of the working memory task.

* equals significance of $p \leq 0.05$ in a comparison of lithium or valproate group to placebo.



Spatial Attention Task:

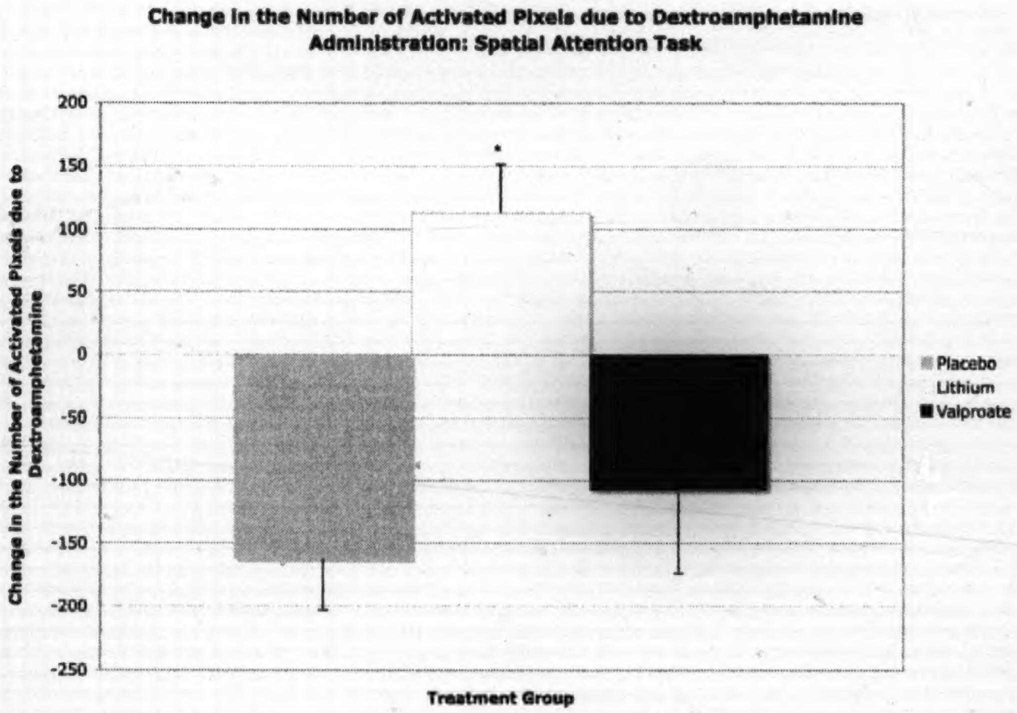
There was a treatment effect observed for the change in the number of activated pixels (df = 2, F = 9.46, $p < 0.001$) (Figure 4.2). *Post hoc* Bonferroni corrections for multiple comparisons revealed a significant difference between the placebo and lithium groups (p = 0.000). A significant increase in the mean change in the number of activated pixels due to dextroamphetamine administration was observed in the lithium group, compared to the placebo group (placebo = -162.27 ± 40.9; lithium = 113.05 ± 38.8; $p < 0.001$).

Eight regions, including occipital gyri, lingual gyri, parietal gyri and cuneus were analyzed for *post hoc* between-group differences in the change in fMRI response due to dextroamphetamine administration during performance of the task. There was a significant increase in the number of activated pixels in the lithium group compared to the placebo group in the cuneus, the left middle occipital gyrus, left ligual gyrus and the right lingual gyrus (Table 4.1).

No significant treatment effect was observed between groups in a one-way ANOVA of the mean change in the BOLD signal magnitude (df = 2, F = 2.07, p = 0.1); therefore no *post-hoc* ROI analysis was performed.

Figure 4.2: Graph showing the mean change (± S.E. error bars) in the number of activated pixels due to dextroamphetamine administration for each treatment group (placebo, lithium, valproate) during performance of the spatial attention task.

* equals significance of $p \leq 0.05$ in a comparison of lithium or valproate group to placebo.



Word Generation Paradigm:

There was a treatment effect observed for the change in the number of activated pixels (df = 2, F = 7.29, p = 0.001) (Figure 4.3). *Post hoc* Bonferroni corrections for multiple comparisons revealed a significant difference between the placebo and lithium groups (p = 0.005). A significant increase in the mean change in the number of activated pixels due to dextroamphetamine administration was observed in the lithium group, compared to the placebo group (placebo = -46.76 ± 24.1; lithium = 88.16 ± 32.5; p = 0.001)

In the lithium group one ROI, the left and right superior parietal gyri demonstrated a significant difference in the change in the number of activated pixels following dextroamphetamine administration compared to the placebo group. There was a trend to significance observed between the lithium and placebo groups in the left inferior parietal lobe (Table 4.1).

There was a significant group effect observed in the change in the percent BOLD signal (df = 2, F = 10.971, p< 0.001). *Post hoc* Bonferroni corrections for multiple comparisons revealed a significant difference between the placebo and lithium groups (p = 0.000). The mean change in the BOLD signal magnitude was significantly greater in the lithium group compared to the placebo group (placebo = -0.057 ± 0.05; lithium = 0.275 ± 0.07; p < 0.001). The change in percent BOLD signal due to dextroamphetamine administration was significantly different between the lithium and placebo groups in the left and right inferior parietal gyrus, the right dorsolateral prefrontal cortex, the left superior parietal gyrus and the right superior temporal gyrus. The valproate group also had statistically significant differences from the placebo group, with significant changes in the BOLD signal in the left inferior parietal gyrus and right precentral gyrus following dextroamphetamine, (Table 4.2).

Figure 4.3: Graph showing the mean change (± S.E. error bars) in the number of activated pixels due to dextroamphetamine administration for each treatment group (placebo, lithium, valproate) during performance of the verbal task.

* equals significance of $p \leq 0.05$ in a comparison of lithium or valproate group to placebo.

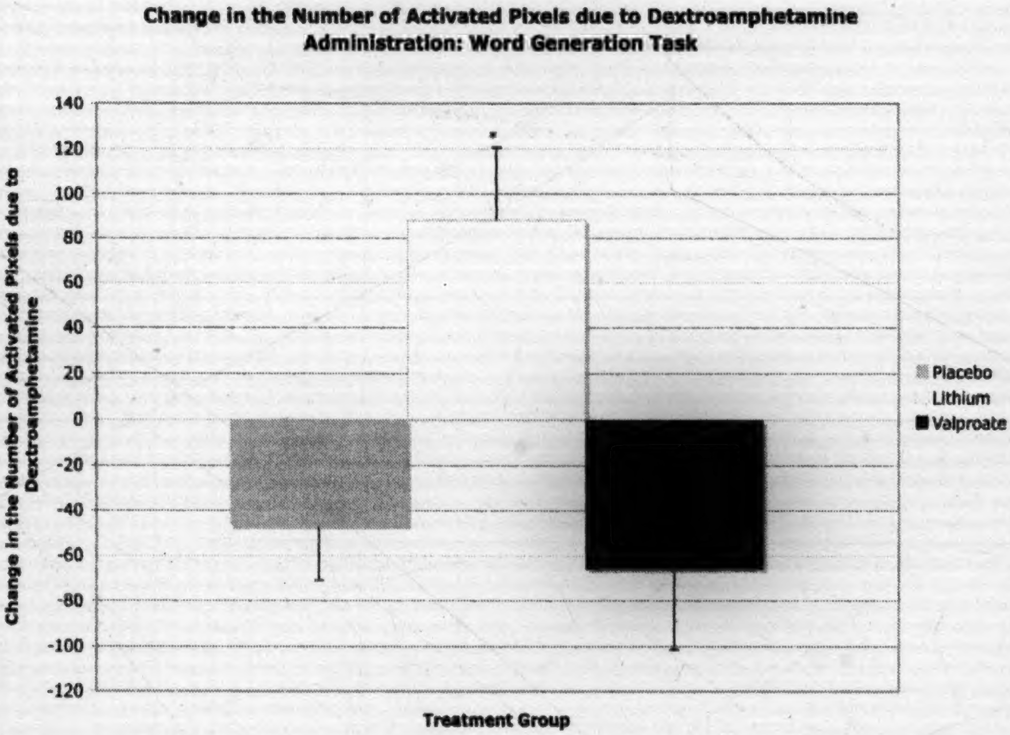


Table 4.1: Change in the number of activated pixels following dextroamphetamine administration

The table shows the change in the number of activated pixels due to amphetamine administration in the working memory task, the spatial attention task and the word generation paradigm (mean ± SEM). There are three treatment groups: placebo, lithium and valproate.

* = significant differences of $p \leq 0.05$ between placebo and lithium groups (** trend to significance)

† = significant differences of $p \leq 0.05$ between placebo and valproate groups (†† trend to significance)

Regions of interest for tasks: **working memory task**: right insula (RINS), left inferior pariteal gyrus (LIP), right inferior parietal gyrus (RIP), left superior parietal gyrus (LSP), right superior parietal gyrus (RSP), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIF), left middle frontal gyrus (LMF), right middle frontal gyrus (RMF), left superior frontal gyrus (LSF), right superior frontal gyrus (RSF), left inferior occipital gyrus (LIOG), right inferior occipital gyrus (RIOG), left precentral gyrus (LPCG), right precentral gyrus (RPCG), left insula (LINS) and cingulate gyrus (CING); **spatial attention task**: cuneus (CUN), left middle occipital gyrus (LMOG), right middle occipital gyrus (RMOG), left lingual gyrus (LLG), right lingual gyrus (RLG), right superior parietal gyrus (RSP), precuneus (PRECUN), left superior parietal gyrus (LSP), right middle occipital gyrus (RMOG); **word generation paradigm**: left inferior parietal gyrus (LIP), left superior parietal gyrus (LSP), right inferior parietal gyrus (RIP), right superior parietal gyrus (RSP), broca's area (BRO), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left precentral gyrus (LPCG), right precentral gyrus (RPCG), cingulate gyrus (CING), supplementary motor area (SMA), left superior temporal gyrus (LST), right superior temporal gyrus (RST), thalamus (THA).

	ROI	PLACEBO GROUP	LITHIUM GROUP	VALPROATE GROUP	p-value vs placebo * & †
Memory Task	RINS	-55.67 ± 44.0	3.29 ± 16.7	97.33 ± 59.0 ††	0.056
	LIP	-19.78 ± 94.4	-90.57 ± 64.1	67.56 ± 109.3	
	RIP	-36.89 ± 25.08	0.29 ± 0.2	34.22 ± 27.1	
	LSP	-37.67 + 52.9	-12.86 ± 20.6	-1.00 ± 45.4	
	RSP	-45.22 ± 26.7	-1.29 ± 5.5	2.67 ± 8.7	
	LDLPFC	-54.89 ± 22.0	-65.86 ± 48.8	-53.78 ± 52.8	
	RDLPFC	-98.44 ± 81.5	-32.43 ± 28.6	42.11 ± 21.9	
	LIF	-171.8 ± 111.5	-201.42 ± 116.1	-84.67 ± 51.2	
	RIF	-83.68 ± 60.7	-10.12 ± 25.3	20.11 ± 13.1	
	LMF	-117.89 ± 39.5	-90.00 ± 65.4	-64.22 ± 69.1	
	RMF	-174.33 ± 146.8	-43.71 ± 33.1	52.00 ± 26.0	
	LSF	-53.11 ± 27.8	-46.29 ± 24.5	-34.67 ± 25.3	
	RSF	-50.22 ± 50.5	-8.14 ± 9.3	19.78 ± 11.9	
	LIOG	-81.67 ± 63.5	-41.14 ± 49.7	-73.33 ± 29.9	
	RIOG	-87.78 ± 47.5	-69.43 ± 51.7	-62.67 ± 36.8	
	LPCG	-161.78 ± 80.7	-143.71 ± 90.5	-104.33 ± 92.5	
	RPCG	-64.78 ± 54.1	14.00 ± 12.3	16.89 ± 10.4	
	LINS	-73.22 ± 63.7	-34.14 ± 26.2	-8.11 ± 16.1	
	CING	-87.78 ± 52.8	-32.14 ± 25.1	-15.56 ± 17.1	
Reaction Task	CUN	-327.67 ± 146.5	281.13 ± 208.5 *	-277.57 ± 298.8	0.033
	LMOG	-98.11 ± 79.4	150.38 ± 62.7 *	-171.14 ± 115.7	0.027
	LLG	-260.00 ± 79.2	323.50 ± 148.3 *	-370.43 ± 226.2	0.005
	RLG	-155.56 ± 65.2	154.00 ± 99.4*	-287.71 ± 191.2	0.023
	RSP	-118.78 ± 111.7	1.88 ± 28.3	210.43 ± 111.2 ††	0.056
	PRECUN	-289.67 ± 202.9	-16.25 ± 90.6	91.57 ± 129.6	
	LSP	-32.89 ± 104.9	48.13 ± 21.1	60.43 ± 76.8	
	RMOG	-34.11 ± 36.9	-38.38 ± 29.2	-121.71 ± 199.7	
Verbal Task	LIP	-122.89 ± 114.7	301.00 ± 165.3 **	88.43 ± 87.2	0.059
	LSP	65.50 ± 65.0	345.43 ± 133.1 *	62.43 ± 73.4	0.015
	BRO	-210.63 ± 118	-67.14 ± 312.1	-419.86 ± 265.5	
	LDLPFC	-61.25 ± 46.4	2.71 ± 43.7	-146.57 ± 130.0	
	RDLPFC	12.00 ± 31.5	39.14 ± 17.8	-26.86 ± 81.4	
	RIP	-38.38 ± 19.8	39.00 ± 35.9	-1.29 ± 63.8	
	RSP	-43.88 ± 25.2	76.00 ± 52.3	16.57 ± 72.1	
	LPCG	-228.25 ± 135.8	132.71 ± 199.2	-239.57 ± 257.3	
	RPCG	21.00 ± 23.4	66.14 ± 36.8	-40.00 ± 62.7	
	CING	-36.00 ± 75.2	104.71 ± 63.8	-32.86 ± 92.1	
	SMA	-125.25 ± 154.1	109.29 ± 126.8	32.86 ± 173.0	
	LST	181.25 ± 105.3	83.57 ± 43.5	-176.57 ± 154.5	
	RST	139.38 ± 87.8	-0.57 ± 5.41	-8.86 ± 18.5	
	THA	-76.25 ± 51.36	2.29 ± 3.4	-4.57 ± 8.11	

Table 4.2: Change in the BOLD signal following dextroamphetamine administration

The change in the magnitude of the BOLD response due to amphetamine administration; in the working memory task, the reaction task and the verbal task (mean ± SEM). There are three treatment groups: placebo, lithium and valproate.

* = significant differences of $p \leq 0.05$ between placebo and lithium groups

† = significant differences of $p \leq 0.05$ between placebo and valproate groups

Regions of interest for tasks: **working memory task**: right insula (RINS), left inferior pariteal gyrus (LIP), right inferior parietal gyrus (RIP), left superior parietal gyrus (LSP), right superior parietal gyrus (RSP), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIF), left middle frontal gyrus (LMF), right middle frontal gyrus (RMF), left superior frontal gyrus (LSF), right superior frontal gyrus (RSF), left inferior occipital gyrus (LIOG), right inferior occipital gyrus (RIOG), left precentral gyrus (LPCG), right precentral gyrus (RPCG), left insula (LINS) and cingulate gyrus (CING); **spatial attention task**: cuneus (CUN), left middle occipital gyrus (LMOG), right middle occipital gyrus (RMOG), left lingual gyrus (LLG), right lingual gyrus (RLG), right superior parietal gyrus (RSP), precuneus (PRECUN), left superior parietal gyrus (LSP), right middle occipital gyrus (RMOG); **word generation paradigm**: left inferior parietal gyrus (LIP), left superior parietal gyrus (LSP), right inferior parietal gyrus (RIP), right superior parietal gyrus (RSP), broca's area (BRO), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left precentral gyrus (LPCG), right precentral gyrus (RPCG), cingulate gyrus (CING), supplementary motor area (SMA), left superior temporal gyrus (LST), right superior temporal gyrus (RST), thalamus (THA).

	ROI	PLACEBO GROUP	LITHIUM GROUP	VALPROATE GROUP	p-value vs placebo *
Memory Task	RSP	-0.26 ± 0.1	-0.24 ± 0.1	0.12 ± 0.1	
	LIP	-0.30 ± 0.1	-0.08 ± 0.1	-0.03 ± 0.2	
	RIP	-0.06 ± 0.1	-0.08 ± 0.1	0.06 ± 0.1	
	LSP	-0.17 ± 0.1	0.03 ± 0.1	-0.16 ± 0.1	
	LDLPFC	-0.14 ± 0.2	-0.25 ± 0.2	-0.02 ± 0.2	
	RDLPFC	0.05 ± 0.2	-0.16 ± 0.2	0.03 ± 0.1	
	LIF	-0.18 ± 0.1	-0.33 ± 0.2	-0.09 ± 0.1	
	RIF	0.04 ± 0.1	-0.01 ± 0.2	0.05 ± 0.2	
	LMF	-0.19 ± 0.1	-0.39 ± 0.1	-0.17 ± 0.1	
	RMF	0.08 ± 0.2	-0.17 ± 0.2	0.06 ± 0.1	
	LSF	-0.38 ± 0.2	-0.17 ± 0.1	-0.29 ± 0.1	
	RSF	-0.07 ± 0.2	-0.15 ± 0.2	0.04 ± 0.1	
	LIOG	-0.02 ± 0.2	-0.05 ± 0.2	-0.36 ± 0.2	
	RIOG	-0.37 ± 0.2	-0.20 ± 0.2	-0.23 ± 0.2	
	LPCG	-0.25 ± 0.2	-0.25 ± 0.2	-0.30 ± 0.1	
	RPCG	-0.21 ± 0.1	0.01 ± 0.2	-0.11 ± 0.1	
	LINS	-0.24 ± 0.1	-0.08 ± 0.2	0.10 ± 0.2	
	RINS	0.09 ± 0.2	-0.02 ± 0.2	0.53 ± 0.3	
	CING	-0.17 ± 0.1	-0.18 ± 0.3	-0.04 ± 0.1	
Reaction Task	LLG	-0.47 ± 0.2	-0.08 ± 0.1*	-0.32 ± 0.3	
	PRECUN	0.05 ± 0.2	0.17 ± 0.3	0.31 ± 0.3	
	CUN	-0.37 ± 0.11	0.18 ± 0.3	-0.10 ± 0.4	
	LSP	-0.17 ± 0.2	-0.01 ± 0.3	0.28 ± 0.2	
	RSP	-0.09 ± 0.1	0.19 ± 0.2	0.05 ± 0.3	
	LMOG	0.10 ± 0.1	0.09 ± 0.2	0.01 ± 0.3	
	RMOG	-0.16 ± 0.1	-0.15 ± 0.1	-0.47 ± 0.2	
	RLG	-0.29 ± 0.2	0.04 ± 0.3	-0.32 ± 0.4	
Verbal task	*RDLPFC*	-0.12 ± 0.2	0.42 ± 0.3 *	-0.24 ± 0.4	0.014
	LIP	-0.53 ± 0.2	0.47 ± 0.4*	0.45 ± 0.4 †	0.037 for lith 0.04 for valp
	RIP	-0.36 ± 0.3	0.37 ± 0.2 *	0.06 + 0.2	0.051
	LSP	-0.10 ± 0.2	0.80 ± 0.3 *	0.13 ± 0.1	0.034
	LDLPFC	0.11 ± 0.3	0.05 ± 0.3	-0.09 ± 0.2	
	BRO	0.24 ± 0.1	0.51 ± 0.3	-0.39 ± 0.3	
	RSP	-0.10 ± 0.2	0.44 ± 0.2	-0.12 ± 0.1	
	LPCG	0.08 ± 0.2	0.07 ± 0.2	-0.34 ± 0.1	
	RPCG	-0.03 ± 0.1	0.17 ± 0.2	-0.25 ± 0.06 †	0.043
	CING	0.15 ± 0.1	0.25 ± 0.2	-0.10 ± 0.3	
	SMA	-0.08 ± 0.2	0.22 ± 0.2	-0.21 ± 0.2	
	LST	-0.02 ± 0.3	0.23 ± 0.2	-0.28 ± 0.3	
	RST	0.22 ± 0.2	-0.30 ± 0.2 *	0.02 ± 0.1	0.047
	THA	-0.22 ± 0.2	0.16 ± 0.2	-0.16 ± 0.3	

4.4 Discussion

We have previously found that a 25 mg dose of dextroamphetamine in healthy volunteers causes a region-specific and task-dependent decrease in the number of activated pixels and the percent BOLD signal during working memory, verbal, and spatial attention tasks (Willson et al., 2004). The present study confirms these findings. In addition it demonstrates that these effects can be partially attenuated by pre-treatment with either lithium or valproate. This is the first human evidence to suggest that both lithium and valproate may have a similar effect on regional brain activation.

Dextroamphetamine acts to increase the release of catecholamines from neuronal terminals, resulting in increased concentration of dopamine and noradrenaline in the synapse (Masand and Tesar, 1996). It is conceivable, therefore, that any effects of lithium and valproate could be due to direct attenuation of the effects following release of these neurotransmitters, particularly dopamine. Certainly there is some support for suggestions that dopamine-induced changes can be attenuated by chronic treatment with lithium in animal studies (Cox et al., 1971; Flemenbaum , 1977; Barnes et al., 1986) (although this was not observed in all studies (Cappeliez and Moore, 1990)), and may also inhibit amphetamine-induced behaviors (Lerer et al., 1984). There is also some evidence that in animals chronic lithium may reduce dopamine release in response to amphetamine or cocaine (Berggren, 1985; Gambarana et al., 1999). In contrast, other studies showed either no change in dopamine release (Aylmer et al., 1987) or an increase in some brain regions (Baptista et al., 1993), following amphetamine administration. In addition, there is some evidence showing that valproate may reduce dopaminergic responses following acute administration (Cao and Peng, 1993; Agmo et al., 1996; Ralph-Williams et al., 2003) and increase basal dopamine concentrations at lower doses (Murakami et al., 2001). Nonetheless, other studies suggest that acute valproate may increase dopamine release in some brain regions (Ichikawa and Meltzer, 1999). Taken together, this evidence does not convincingly suggest that the findings of the current study are due to direct attenuation of amphetamine-induced dopamine release by either lithium or valproate. Furthermore, this is supported by the clinical findings that, unlike dopamine antagonists, lithium does not have efficacy in the clinical treatment of schizophrenia (Johnstone et al., 1988). Given this, it is likely that attenuation of dextroamphetamine-induced changes by both lithium and valproate is via a mechanism "downstream" to the release of noradrenaline and dopamine. We propose that these dextroamphetamine-induced changes may in part be mediated by effects upon the PI-cycle, and that these in turn may be attenuated by the effects of pre-treatment with lithium and valproate upon the PI-cycle.

The dextroamphetamine-induced increase in the release of dopamine and noradrenaline may increase activity of a number of second messenger systems (including the PI second messenger system (via activation of dopamine on the D_1 receptor subtype or of noradrenaline on the α_{1A} and α_{1B} receptor subtypes) (Fisher et al. 1992). Previous studies have confirmed that dextroamphetamine administration acts indirectly to stimulate the PI-cycle (Yu et al., 2003; Silverstone et al., 2002; Barkai et al., 1981). Thus, some of the decrease in brain activation following dextroamphetamine may be mediated via the PI-cycle.

It has long been hypothesized that the clinical effectiveness of lithium as a mood stabilizer may be mediated through its actions on the PI-cycle, where it inhibits the enzyme inositol monophosphatase (Atack, 1995; Berridge and Irvine, 1989; Renshaw, 1986; Bone et al., 1992). The resulting depletion of *myo*-inositol is proposed to decrease the activity of the PI-cycle. The best method of testing this hypothesis *in vivo* is by using magnetic resonance spectroscopy (MRS), and in general studies to date have been supportive of this hypothesis (Silverstone et al., 2004).

The mechanism of action of valproate on the PI-cycle has been less well examined. While valproate does not directly inhibit inositol monophosphatase (Vadnal and Parthasarathy, 1995), there is increasing evidence suggesting that valproate affects the PI cycle. Sodium valproate has been observed to cause inositol depletion in yeast cell cultures after acute and chronic treatment (Vaden et al., 2001; Ju and Greenberg, 2003). Moreover, both lithium and valproate have demonstrated a common effect upon growth cone development in the amoeba *Dictyostelium*, which the authors contend is consistent with the hypothesis that both drugs cause inositol depletion (Williams et al., 2002), and both have been shown to decrease inositol uptake at high inositol concentrations in human astrocytomas (Wolfson et al., 2000). Additionally, both lithium and valproate decrease expression of the gene, which encodes for inositol monphosphatase (Murray and Greenberg, 2000) and both cause a decrease in *myo*-inositol in rat brain as measured by MRS (O'Donnell et al., 2000). Overall, therefore, the evidence to date suggests that valproate may decrease PI-cycle activity to the same degree as lithium (Williams et al., 2002; Ju and Greenberg, 2003; O'Donnell et al., 2000; Wolfson et al, 2000; Vaden et al, 2001; Dixon and Hokin 1997; Li et al, 1993), presumably acting via a different mechanism.

In conclusion, the present study demonstrates that dextroamphetamine reduces brain activation in a region- and task- specific manner. These changes can be partially attenuated by pre-treatment with either lithium or valproate, with the effects of each of these drugs differing somewhat. It is likely that some of the actions of dextroamphetamine are mediated by actions on the PI-cycle, and it is also likely that this attenuation by lithium and valproate of these dextroamphetamine effects represent actions of both drugs on the PI-cycle.

(A version of this chapter has been published – see Bell et al. (2005) Human Psychopharmacol, 20: 87-96)

We have confirmed that a single dextroamphetamine dose in healthy controls causes a decrease in regional brain activity. Pretreatment with either lithium or valproate, therapy for acute mania in bipolar patients, effectively attenuates the dextroamphetamine effect, although not on all tasks or in all regions. This supports a similar mechanism of action of the two drugs in modulating regional brain activity during cognition.

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Chapter 5. Valproate attenuates dextroamphetamine-induced subjective changes more than lithium.

5.1 Introduction

Patients in the manic phase of BP frequently exhibit symptoms of irritability, euphoria, grandiosity, racing thoughts, hyperactivity, distractibility, and reduced need for sleep (Goodwin and Jamison, 1990; Fogarty et al. 1994). These symptoms are similar to those reported by normal volunteers after administration of dextroamphetamine, particularly increased alertness, increased mood, racing thoughts, restlessness, distractibility, and decreased need for sleep (Jacobs and Silverstone, 1986; Angrist et al., 1987; Zacny et al., 1992; Brauer and de Wit, 1996). In addition, dextroamphetamine administration causes an increase in heart rate, blood pressure, and cortisol levels similar to the changes associated with mania (Jacobs and Silverstone, 1986). These qualities have lead researchers to propose that dextroamphetamine may be a model for mania. However, although dextroamphetamine causes similar subjective and physiological changes, it is unclear if the biological mechanisms resulting in the symptomatology are comparable to those involved in a manic phase in patients suffering from bipolar disorder. One way of determining its utility is to see if drugs, which effectively attenuate manic episodes, also attenuate dextroamphetamine-induced changes.

Previously, one week of lithium pre-treatment has been shown to be insufficient to attenuate the subjective and physiological effects of dextroamphetamine administration in healthy volunteers (Silverstone et al., 1998). The fact that lithium, a commonly prescribed mood stabilizer, fails to significantly protect subjects from the effects of dextroamphetamine seems to suggest that the dextroamphetamine model of mania is not equivalent to the mania experienced by patients. It has been suggested, however, that because the clinical efficacy of lithium may extend beyond one week, a one-week treatment study may be insufficiently short to demonstrate a drug effect (Silverstone et al., 1998). Nonetheless, animal studies of an amphetamine hyperactivity model have not demonstrated an effect of acute or chronic lithium administration in the attenuation of activity behaviors in rats caused by administration of dextroamphetamine (Cappeliez and Moore, 1990; Aylmer et al., 1987).

The other widely used mood stabilizer for BP is valproate, but to date there have been no studies examining the effects of valproate pre-treatment on dextroamphetamine-induced changes in humans. In animals studies, an attenuation of hyperactivity with acute valproate pretreatment has been seen (Cao and Peng, 1993). More recently, in mice with a dysregulated dopamine system, an attenuation of hyperactivity has also been noted with valproate pretreatment (Ralph-Williams et al., 2003).

In the present study we have therefore evaluated the effect of lithium and valproate pre-treatment on the dextroamphetamine-induced subjective and physiological changes in healthy controls. This may help understand the usefulness of dextroamphetamine as a model for mania.

5.2 Materials and Methods

Approval for the study was obtained from the Ethics Review Committee of the University of Alberta, and all subjects gave full informed consent.

5.2.1 Subjects

Thirty-three subjects, aged 18 – 48, were recruited by poster advertisement to participate in the study. Using a semi-structured psychiatric interview schedule (SCID,) participants were screened for past or present history of psychiatric illness as well as history of psychiatric illness in their immediate family. Any history of this led to exclusion. Past medical history and abuse of alcohol, nicotine, caffeine or drugs were also determined, and subjects were excluded based on current abuse of these substances. Subjects who used any recreational drugs in the past six months (one year for stimulants such as amphetamine) were also excluded. At screening, a full medical history was obtained from all subjects and a medical examination was performed. Subjects were required to fast from midnight the day prior to testing and abstain from caffeinated beverages and cigarettes.

5.2.2 Study Design

A double-blind placebo controlled study design was used in which subjects received either lithium (900mg daily), sodium valproate (500mg for 3 days; 1000mg daily thereafter), or placebo (lactose powder) for 14 days (*n = 9, n = 12, n = 12* respectively). Serum lithium and sodium valproate levels were measured on the morning of day 14.

Subjective measurements were assessed using 100-mm visual analog scales (VAS) (Folstein and Luria, 1973) for feelings of happiness, energy, hunger, restlessness, alertness, light-headedness, irritability, concentration, speed of thoughts, anxiety, and physical well-being. For each of these measures one end of the scale was marked "I do not feel ……" and the other was marked "I feel the most ………… I have ever felt". These were alternated so that on some measures the text with "I do not feel ……" was on the left hand side of the line and on others it was on the right hand side of the line. These measures have been shown to be sensitive to the changes induced by psychostimulants such as dextroamphetamine as well as the mood changes seen in mania (Fischman and Foltin, 1991). The VAS were measured at baseline (t = 0 min) and twice after the administration of a single oral dose of 25 mg dextroamphetamine (t = 75 min and t = 120 min). The dose of 25 mg was selected based on previous reports (Angrist et al., 1987; Dommisse et al., 1984) and our own experience with this dose (Asghar et al., 2003). Physiological measurements of heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were obtained at the same time intervals immediately following the VAS. This timing was chosen to match the peak subjective response to dextroamphetamine (Silverstone et al 1998, 2002), which occurs 60 – 120 minutes after administration.

5.3 Results

5.3.1 Subjects

A total of 33 subjects who met the eligibility criteria took part in the study. Twelve subjects received placebo, 9 received lithium, and 12 received sodium valproate. A chi-square test revealed a significant sex difference in the sample (females = 10, males = 23). There were no significant differences in the groups with respect to age (placebo mean age 25.8 ± 5.9 years, lithium 25.8 ± 8.7 years, valproate 27.1 ± 6.2 years) or weight (placebo mean weight 160.8 ± 30.5 pounds, lithium 169.4 ± 22.8 pounds, valproate 166.7 ± 26.4 pounds). Serum drug plasma levels measured on day 14 confirmed compliancy with the medication regime (plasma level lithium, 0.39-0.77 mmol/L; plasma level valproate, 0.52-0.88 mmol/L).

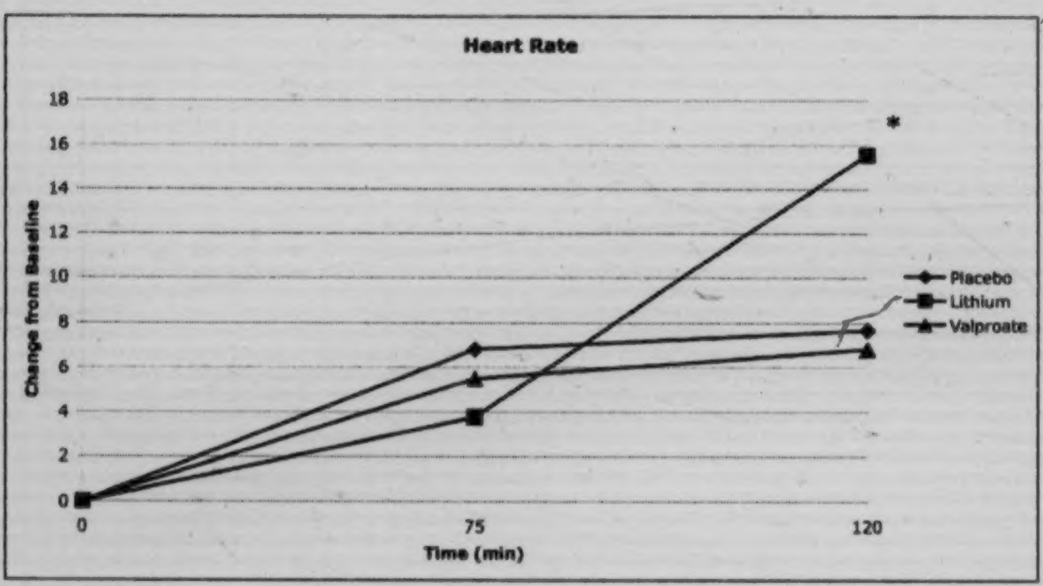
5.3.2 Physiological Measures

Dextroamphetamine administration caused a significant increase in heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP). There was a main time effect on heart rate ($F_{1,29} = 5.15$, $p = 0.03$) and a group effect on DBP ($F_{2,29} = 4.55$, $p = 0.02$) and SBP ($F_{2,29} = 3.87$, $p = 0.03$) (Figure 1). Post-hoc paired sample t-tests revealed that all three physiological measures (DBP, SBP and HR) were significantly increased from baseline at both measurement times post-dextroamphetamine administration (t = 75 min and 120 min). There was a significant group and time interaction for heart rate ($F_{1,29} = 13.25$, $p < 0.00$). *Post hoc* independent sample t-test analysis revealed a significantly increased heart rate from baseline at 120 min in the lithium group compared to the placebo group (p=0.002) (Figure 5.1). There was a main effect of gender on the SBP ($F_{1,29}$ = 5.26, p = 0.03). This was the only physiological measure by which a gender effect was observed. *Post hoc* independent t-test analysis revealed a significantly increased SBP change at 120 min in the lithium group compared to the valproate group (p =0.04) (Figure 5.1).

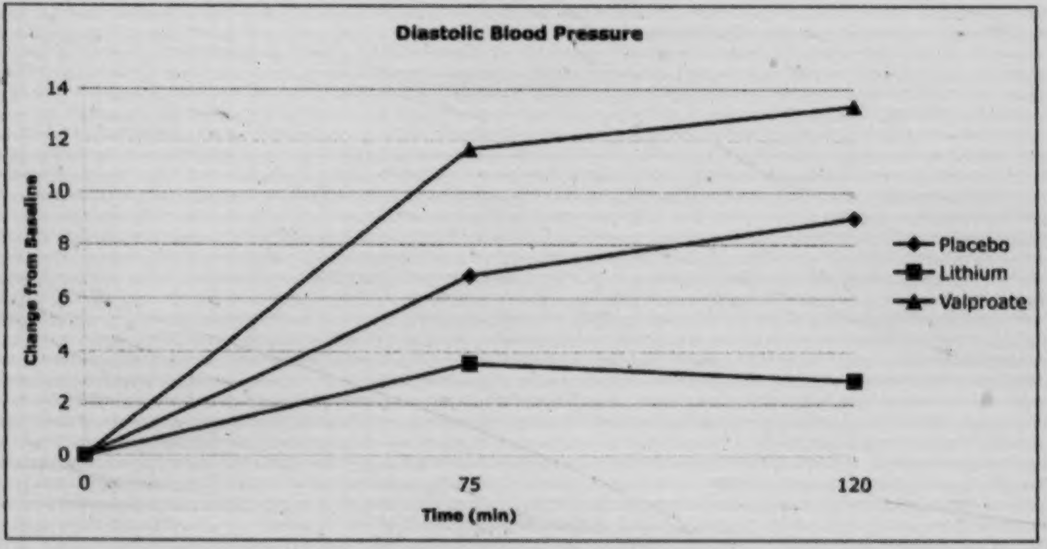
Figure 5.1: Effect of dextroamphetamine on groups pre-treated with placebo (♦), lithium (■), or sodium valproate (▲) for heart rate (A), diastolic blood pressure (B), and systolic blood pressure (C)

*** is significant vs. placebo group at $p \leq 0.05$ level of significance and ** is significant vs. valproate group at $p \leq 0.05$ level of significance.**

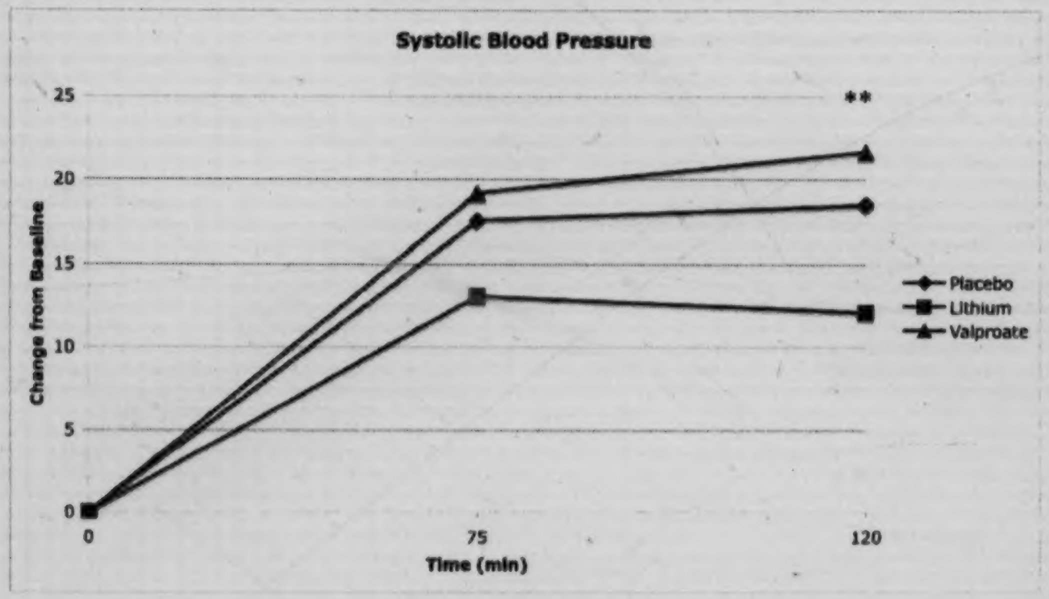
A.



B.


Diastolic Blood Pressure
14
12
10
8
6
4
2
0
Change from Baseline
0
75
120
Time (min)
Placebo
Lithium
Valproate

C.


Systolic Blood Pressure
25
20
15
10
5
0
Change from Baseline
**
0
75
120
Time (min)
Placebo
Lithium
Valproate

5.3.3 Subjective Measures

There was a main group effect on the change from baseline in the subjective measures of happiness, energy, alertness, light-headedness following dextroamphetamine in healthy volunteers (Table 5.1). *Post-hoc* analysis, in the form of paired sample t-tests, showed a significant increase from baseline in the subjective measures for energy, restlessness, alertness, lightheadedness, concentration and speed of thought at both time periods post dextroamphetamine (t = 75 min, and t = 120 min). *Post-hoc* independent t-tests of measures with a significant group effect showed that there were no significant differences between the treatment groups on change at either 75min or 120 min. *Post-hoc* independent t-test analysis of the group interactions revealed a significantly smaller increase from baseline in measures of happiness, energy alertness and lightheadedness in the valproate group compared to the placebo group (Figure 5.2). In contrast, for lithium there was only one significant difference between the placebo and lithium groups, noted 75 min after dextroamphetamine administration on the happiness measure (Figure 5.2a), although there was a non-significant trend towards decreased energy (Figure 5.2b).

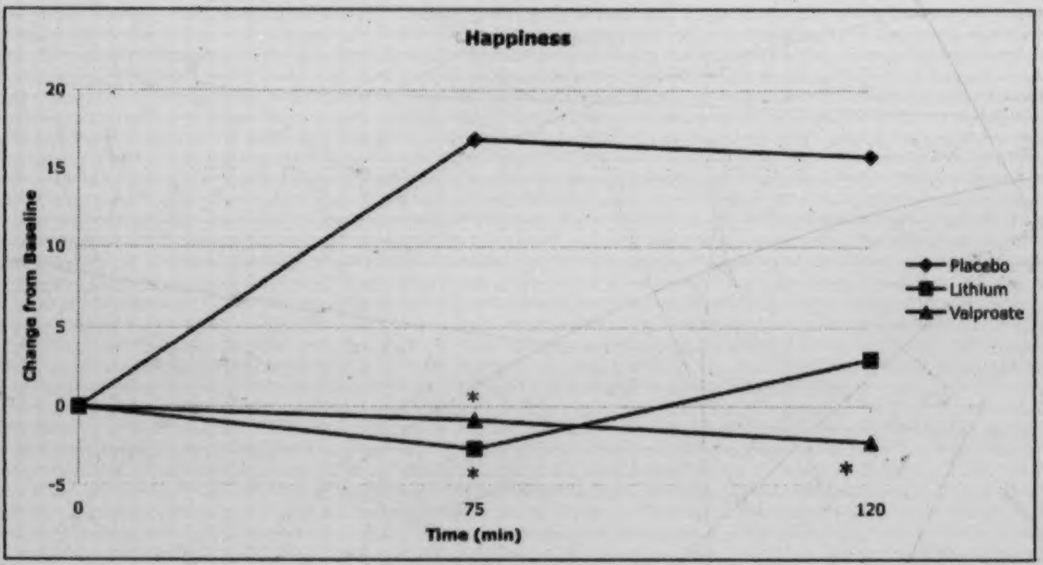
Table 5.1: F_{df} values from repeated measures ANOVA on subjective VAS measures

Measure	Main effect of time ($F_{1,29}$)	Main effect of group ($F_{2,29}$)	Group x time interaction ($F_{2,29}$)	*Post Hoc* Student's t-tests for main effect of group and group x time interaction
Happiness	0.11	4.57*	0.95	Change 75 min Valproate vs. Placebo p = 0.012 Change 120 min Valproate vs Placebo p = 0.028 Change 75 min Lithium vs Placebo p = 0.020
Energy	0.01	3.53*	1.75	Change 75 min Valproate vs. Placebo p = 0.009 Change 120 min Valproate vs Placebo p = 0.009
Hunger	2.12	0.04	2.77	
Restlessness	0.02	0.06	0.02	
Alertness	0.16	4.91*	0.28	Change 75 min Valproate vs. Placebo p = 0.009 Change 120 min Valproate vs. Placebo p = 0.003
Light-headedness	0.11	4.89*	0.14	Change 75 min Valproate vs. Placebo p = 0.014
Irritability	0.12	1.08	0.87	
Concentration	0.11	1.30	0.32	
Speed of Thoughts	0.02	1.71	1.50	
Anxiety	0.003	0.82	0.80	
Physical Well Being	0.36	2.80	0.53	

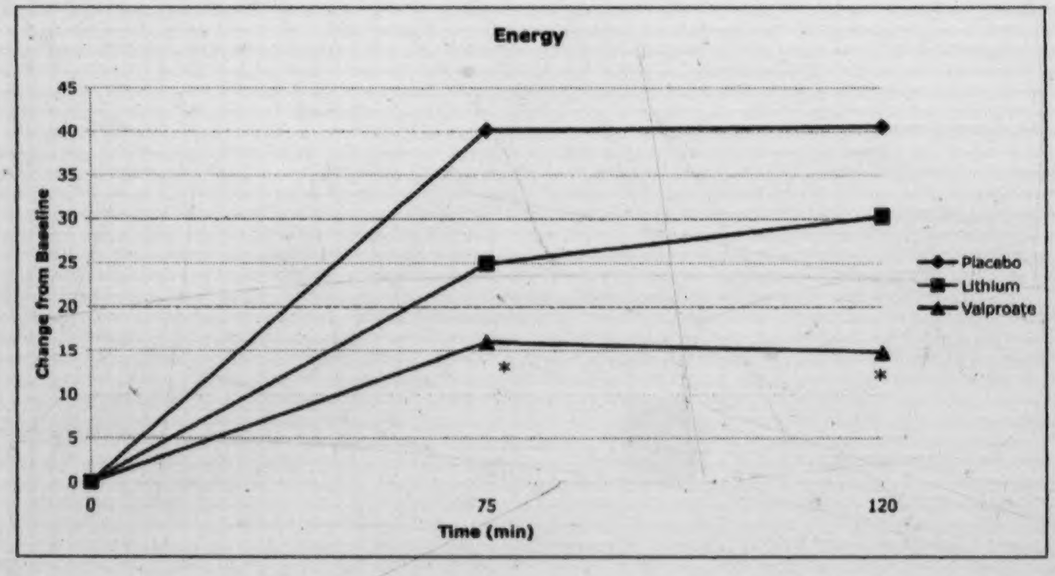
Figure 5.2: Effect of dextroamphetamine on groups pre-treated with placebo (♦), lithium (■), or sodium valproate (▲) on happiness (A), energy (B), alertness (C), and light-headedness (D).

*** is significant vs. placebo group at $p \leq 0.05$ level of significance.**

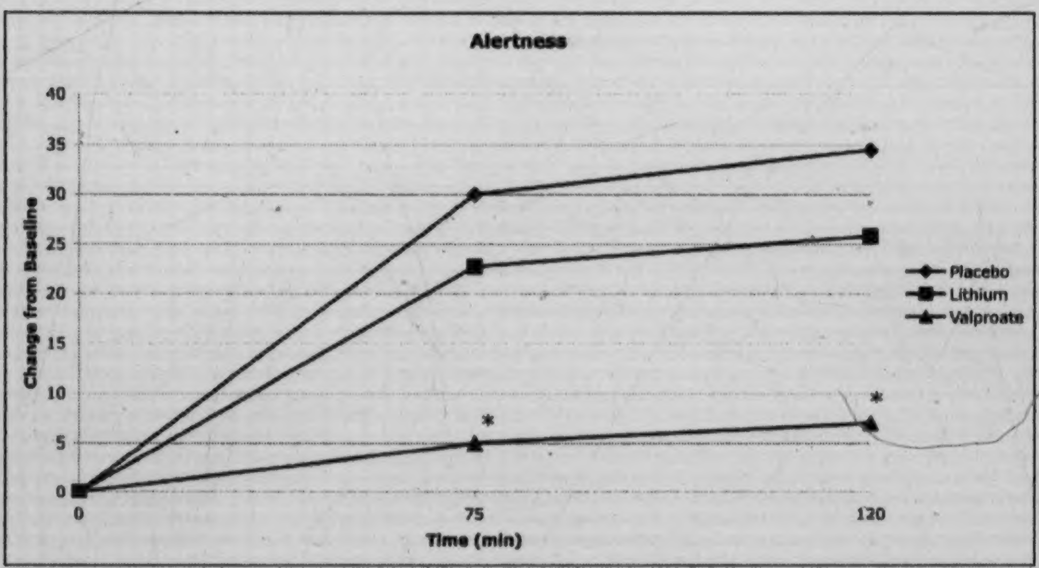
A.



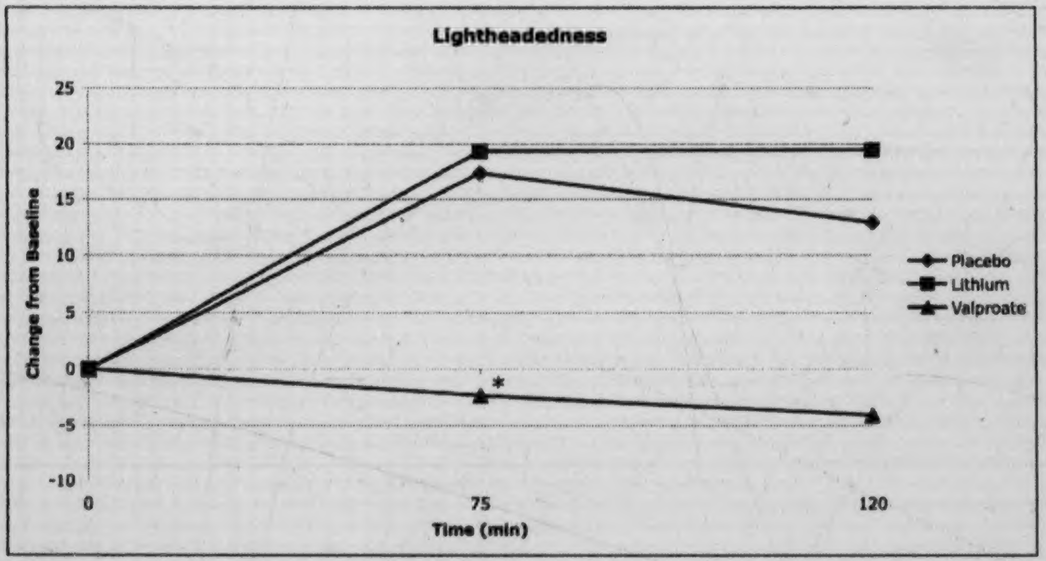
B.


Energy
45
40
35
30
25
20
15
10
5
0
Change from Baseline
0
75
120
Time (min)
*
*
Placebo
Lithium
Valproate

C.


Alertness
40
35
30
25
20
15
10
5
0
Change from Baseline
0
75
120
Time (min)
*
*
Placebo
Lithium
Valproate

D.


Lightheadedness
Change from Baseline
25
20
15
10
5
0
-5
-10
0
75
120
Time (min)
*
Placebo
Lithium
Valproate

5.4 Discussion

The effects of dextroamphetamine on pulse, blood pressure and mood are consistent with those from previous studies, showing a significant increase in systolic and DBP and in feelings of energy, restlessness, concentration, alertness, speed of thought and lightheadedness following dextroamphetamine administration (Silverstone et al., 1983; Dommisse et al., 1984; Rapoport et al., 1978; Hamilton et al., 1983; Silverstone et al., 1998; Asghar et al., 2003). These previous investigations conducted with purely male and mixed gender samples have shown similar dextroamphetamine effects (Dommisse et al., 1984, Silverstone et al., 1983; Silverstone et al., 1998).

Previous studies examining whether or not drugs attenuate dextroamphetamine-induced changes have had mixed results. Administration of the antipsychotic pimozide attenuated dextroamphetamine's effects in one study (Silverstone et al., 1980), but not another (Brauer and de Wit, 1996, 1997). Ondansetron (a 5-HT$_3$ receptor antagonist) showed some attenuation of dextroamphetamine's effects on subjective state and blood pressure (Silverstone et al., 1992; Grady et al., 1996), and a study with the calcium channel antagonist diltiazem found that it only attenuated the cardiovascular, but not subjective, changes (Fabian and Silverstone, 1997). This is of interest since diltiazem has been suggested to be useful in some cases of treatment-resistant bipolar disorder (Silverstone and Birkett, 2000).

Those studies investigating the effect of lithium on dextroamphetamine-induced behaviors have been mixed. A series of three case reports found that there was a lack of subjective amphetamine effects during lithium therapy (Flemenbaum, 1974). Another study examined nine depressed patients, tested before and after 10 days of lithium treatment, and found a 60% reduction in the subjective euphoric and activating effects of dextroamphetamine following treatment with lithium carbonate (van Kammen and Murphy, 1975). In an open-label study in eight unmedicated psychiatric patients, lithium somewhat attenuated the euphoric effects of amphetamine in four patients although not significantly, but did have a significant protective effect against the effects of amphetamine on systolic blood pressure (Angrist and Gershon, 1979). In the only double blind placebo controlled study in healthy volunteers, we found that lithium administration for 7 days did not attenuate the effects of 20 mg dextroamphetamine (Silverstone et al., 1998). The results from the present study also show a mixed pattern, with a significant attenuation of mood elevation, but not of any other subjective measure. Taken together, the literature may suggest that lithium given for at least 10 days has partial effects on mood elevation induced by dextroamphetamine in both patients and volunteers.

Previous animal studies suggest that valproate may attenuate dextroamphetamine-induced behaviors (Ralph-Williams et al., 2003; Cao and Peng, 1993), but to our knowledge there have been no previous human studies. The results from the present study show that valproate significantly attenuates dextroamphetamine-induced changes in happiness, energy, alertness and lightheadedness, although we believe that changes in lightheadedness may have resulted from an adverse effect of medicating with valproate. Subjects in the valproate group reported a significantly greater amount of lightheadedness than the other two groups at baseline, which may account for their decreased responsiveness to dextroamphetamine on this scale.

The mechanism of action by which valproate attenuates a dextroamphetamine effect is uncertain, but one possibility is that valproate may be acting via attenuation of the PI-cycle, since there is increasing evidence that it can attenuate this in both animals (O'Donnell et al, 2000), cell cultures (Williams et al, 2002), and humans (Silverstone et al, 2002a). In this context there is also evidence that dextroamphetamine stimulates the PI-cycle in a dose-dependent manner in animals (Barkai et al., 1981; Yu et al., 2003) as well as in humans (Silverstone et al., 2002b). This is almost certainly an indirect action, since its primary action is to increase extracellular concentrations of dopamine and noradrenaline (Hoebel et al., 1989; Seiden et al., 1993; Karler et al., 1994; Kuczenski & Segal, 1997; Reid et al. 1997). In neurons, the PI-cycle is activated following ligand binding with guanine nucleotide-binding (G_q)-protein coupled receptors, including adrenergic (α_{1A} and α_{1B}), serotonergic (5-HT_{1C} and 5-HT_2), dopaminergic (D_1) and cholinergic (M_1 and M_3) receptor subtypes among others (Fisher et al., 1992). However, there is also good evidence that D_2 activation also affects the PI-cycle and production of inositol triphosphate (Vallar & Meldolesi, 1989; Izquierdo-Claros et al., 1997; Hernandez-Lopez et al., 2000; Tseng & O'Donnell, 2004), and it is therefore likely that a combination of D1, D2, α_{1A} and α_{1B} receptor stimulation accounts for the effects of dextroamphetamine on the PI-cycle. However, the attenuation by valproate of the behavioural effects casued by dextroamphetamine are unlikely to be solely based upon attenuation of the PI-cycle, since this is something that lithium very consistently does

(Berridge et al., 1989; Berridge & Irvine, 1989), and it would therefore be anticipated that both of these drugs would have had similar behavioural effects if PI cycle attenuation was entirely responsible for the mediation of the same behavioural effects. Thus, the mechanism of action by which valproate acts remains uncertain. It is also unclear, to date, the extent of pharmacokinetic and pharmacodynamic interactions between dextroamphetamine and lithium, and dextroamphetamine and valproate. Previously, Markowitz and colleagues (1999) have suggested that dextroamphetamine may be involved in pharmacodynamic interactions between medications, rather than more predominantly pharmacokinetic interactions which occur with methylphenidate. It is not clear if pharmacodynamic interactions between valproate and lithium with dextroamphetamine exist, or if these interactions have themselves have influenced our results.

In conclusion, there appear to be differences in the effects of valproate and lithium on dextroamphetamine-induced effects, and it is conceivable that this may reflect underlying differences in their mechanism of action as mood stabilizers.

(A version of this chapter has been published - see Bell et al.,(2005), Eur Neuropsychopharmacol, 15: 66-69.)

Behaviorally, dextroamphetamine administration in healthy subjects is said to produce a range of subjective effects likened to a manic episode. Pretreatment with two commonly used mood stabilizers, lithium and valproate, has shown differential effects in the attenuation of the subjective effects of dextroamphetamine in healthy controls. It appears that valproate has superior effects in attenuating the subjective effects (and some of the physiological effects) of dextroamphetamine in healthy volunteers.

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Chapter 6. Differential effects of chronic lithium and valproate on brain activation in healthy volunteers.

6.1 Introduction

Individuals suffering from BP suffer from characteristic changes in mood from depression to mania, with variable periods of euthymia. Patients are often treated with mood stabilizers such as lithium or valproate in an attempt to control their affective state. Functional imaging studies have shown that bipolar subjects have altered regional brain activity during cognitive task execution, compared to HCs (Berns et al., 2002; Rubinsztein et al., 2001; Blumberg et al., 1999; Blumberg et al., 2003; Caliguiri et al., 2003; Blumberg et al., 2003; Adler et al., 2004). However, because most patients are medicated at the time of these studies it is difficult to interpret to what extent treatment is responsible for these differences.

To date, there have been few studies to investigate the regional brain effects of valproate in nonpatient samples. Previous PET and SPECT studies investigating CBF effects of valproate have been inconsistent. In baboons, no significant change in CBF was observed with a single dose of valproate (Oliver and Dormehl, 1996); however, CBF is decreased in children treated with sodium valproate (Futagi et al., 1994) and in healthy adults treated for 4 weeks with valproate (Gaillard et al., 1996). In terms of global cerebral metabolic rate, one study has shown a decrease in global cerebral metabolic rate for glucose in normal individuals treated with valproate for 4 weeks (Gaillard et al., 1996). This is consistent with the findings from a study in eight patients with seizure disorders, which showed a decrease in global metabolic rate of glucose after treatment with valproate (Leiderman et al., 1991). This reduction was shown to be region-specific upon ROI analysis (Leiderman et al., 1991). To our knowledge there are no studies which have examined the effects of lithium treatment on CBF or metabolic rate in HC subjects.

Studies in bipolar patients have shown various abnormalities in cerebral metabolism including decreased cerebral metabolic rate in the basal ganglia, frontal and occipital cortices, cortico-limbic areas and increased CGM in the thalamus, amygdala and striatum (Ketter et al, 2000, Buchsbaum et al., 1986). Bipolar depressed patients demonstrate decreased CBF in frontal and limbic areas (Ito et al., 1996) and manic patients display increased CBF in the cingulate and caudate (Blumberg et al., 2000). Functional brain activity measures indicate further dysregulations in bipolar patients in the prefrontal cortices (Blumberg et al., 1999), cingulate and frontal regions (Rubinsztein et al., 2001, Blumberg et al., 2003), limbic areas (Strakowski et al., 2004) and in the motor cortex (Caliguiri et al., 2003, 2004) during the performance of various tasks. A majority of these studies include patients on mood stabilizers and/or other medications. A recent study by Caliguiri and colleagues (2003) has compared a group of bipolar patients off medications (antipsychotics or mood stabilizers), patients on medications, and healthy volunteers and found some significant differences in motor area activation between the groups during a reaction motor task. The authors suggest that the noted increase in activation in the patient group off medication reflects that treatment may have "suppressive effects on specific cortical and subcortical functions" (Caliguiri et al., 2003).

In this study we have examined the BOLD signal magnitude to investigate the effects of two weeks of valproate and lithium treatment in healthy volunteers. By examining the BOLD response, using tasks we have previously shown to be sensitive to drug effects in volunteers (Willson et al., 2004), we are able to observe the regional brain activity effects of these drugs.

6.2 Methods

The ethics board of the University of Alberta Hospital approved this study.

6.2.1 Subjects

Thirty-three right-handed healthy volunteers were recruited through poster advertising from the university community. Subjects underwent a medical exam and medical history, and a detailed semi-structured clinical interview (structured clinical interview for DSM-IV) to rule out past or present psychiatric illness. Past and present drug and alcohol use was assessed and subjects were excluded based on current abuse of these substances. Subjects who had used recreational drugs in the past 6 months, or amphetamine in the past year, were excluded from participating. At 12:01 am the day of the scan, subjects were required to fast until all scans were complete.

6.2.2 Study Design

A double blind study design was used. After a baseline fMRI scan, subjects were randomized to receive capsules containing placebo (lactose powder), lithium (900mg daily), or sodium valproate (500mg for 3 days; 1,000mg daily thereafter) for 14 days prior to a second scan. Nine subjects received lithium, 12 received valproate, and 12 received placebo. At baseline and on day 14, subjects underwent fMRI examinations of the same duration (approx. 45 minutes) in which they performed a working memory task, a word generation paradigm and a spatial attention task. Prior to the second scan, a drug plasma level for those in treatment groups was obtained, which determined serum levels of lithium and valproate. Plasma valproate levels ranged between 0.52-0.88 mmol/L, and plasma lithium levels ranged between 0.39-0.77 mmol/L.

6.2.3 Tasks

Word Generation Paradigm

The verbal task utilized a word generation paradigm in which there were two conditions. In the first condition subjects were asked to repeat the word 'REST' silently until another instruction was given. In the second condition a series of ten single letters randomly chosen from the alphabet were displayed at 4-second intervals. During the display of a single letter, subjects responded by thinking of as many words as possible that begin with that letter and repeating them silently until another letter is presented or the 'REST' instruction appears. The experiment consisted of five 40 second blocks of each condition beginning with 'REST'.

Working Memory Task

The working memory task consisted of two conditions. In the first condition there was a series of 10 arrows pointing to the left or to the right. Subjects responded by pressing the left or right button. In the second condition a 5-digit number was displayed for 4 seconds with the instruction 'Remember this Number'. Immediately after, a series of 10 random single digits was presented. Subjects were asked to respond by pressing one button for yes and one for no if the single digit was or was not in the memorized number. In all, each condition was presented seven times in 24 second blocks pseudo-randomly arranged.

Spatial Attention Task

For this task, subjects were asked to respond as quickly as possible to certain criteria. First, a black cross appeared on the screen. Soon after, the black cross would appear with the target (a black square). Whenever the black cross and square appeared together subjects responded by pressing the button in their dominant hand as fast as possible. The delay between the appearance of the cross and the target was varied randomly from 300 – 1100 ms. Approximately 10% of the trials were actually catch trials designed to ensure subjects were engaged in the task. In a catch trial another black cross-appeared instead of the target and subjects were instructed not to respond. Any responses to catch trials were considered errors, and the error rate could therefore be measured. In this experiment two conditions of the reaction task were alternated to maintain spatial attention (Beauchamp et al 2001; Cabeza and Kingstone 2001). In the first condition the cross and square appeared in the same location (attended location), and in the second condition the target appeared a distance away from the cross (unattended). This task was performed in 10 alternating blocks of each condition, 24 seconds in duration each.

6.2.4 Image Acquisition

All imaging parameters were identical to those described previously (Willson et al., 2004). The fMRI images were collected on a 1.5T Siemens Sonata scanner, using a single shot EPI gradient echo sequence (Memory, Reaction and Verbal Tasks TR = 4010ms, TE = 50ms, 1.7 x 1.7 mm, 4 mm thick) to acquire 30 contiguous slices obtained at an oblique angle along the AC-PC line. A high resolution T1 weighted MPRAGE sequence was also obtained for overlay of the functional analysis.

6.2.5 fMRI Data Analysis

fMRI data analysis were performed according to previously published methods (Willson et al., 2004). Pre-processing and analysis was performed using Statistical Parametric Mapping (SPM), 1999 version (SPM99 - Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during pre-processing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. Sessions with realignment parameters of greater than 4 mm in the direction of translation (along the x,y,z axes) were excluded from the final statistical analysis, as were sessions with motion greater than 0.05 radians in a rotational plane (pitch, roll, yaw). The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 x 8 x 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2* weighted EPI functional images. After normalization, all volumes were resampled to 2 x 2 x 2 mm voxels using trilinear interpolation in space. Finally, all functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between-subject variability and allow Gaussian random field theory to give corrected statistical inferences

(Friston et al 1994). Initial analysis was performed separately for each subject for each task. The model specified for each task was kept identical for all subjects and sessions to create identical design matrices. As part of this analysis three more pre-processing steps were performed using SPM99. First the data were high pass filtered to remove low-frequency drifts in the signal. In addition, the data were low pass filtered using the hemodynamic response function to remove high frequency noise. Effects due to global intensity fluctuations were removed when the data were proportionally scaled to a global mean of 100. The time series for each data set was analyzed according to the general linear model. Previously, we have performed a group analysis on 18 volunteers (Willson et al., 2004) by constructing a fixed effects model for each task. ROIs for each task were then compiled using the most significantly activated voxels from the group average generation maps. ROI images were constructed using automated anatomical labeling (AAL) software (Tzourio-Mazoyer et al., 2002), running with MRIcro software (Rorden and Brett, 2000). We have assessed activation in these same ROIs in the present study.

For each subject, the individual activation maps generated during single-subject analysis were used to identify the change in BOLD signal magnitude. The BOLD signal intensity change was calculated based on regions of interest using the MARSBAR toolbox for SPM (Brett et al 2002) over a seven-voxel sphere centered on the *most* significantly active voxel in each ROI. The fitted response (or BOLD signal intensity change) is expressed in percentage of whole brain mean. Because the global brain mean in the voxel-wise analysis was scaled to 100, this signal change represents the percentage of signal change with respect to the global mean intensity of the scaled images. The number of voxels over which the fitted response was calculated was kept small in order to minimize averaging over non-significant voxels or large veins (Mulderink et al 2002). Subsequently, statistical calculations for BOLD signal magnitude were based on the average response calculated from the plateau portion of the hemodynamic response (eight seconds after stimulus origination until stimulus termination). Values obtained for each ROI during the baseline scan were then subtracted from values obtained at the scan on day 14, after treatment. This resulted in values for the ***change*** in the BOLD response after treatment in all subjects in the three treatment groups for each task, in every ROI. The mean BOLD signal for the groups was calculated from the combined BOLD magnitudes from all the ROIs in each task.

A one-way analysis of variance (ANOVA) was used to assess the treatment effect across groups in each task. *Post-hoc* analyses to correct for multiple comparisons were performed. If significant differences were identified an independent Student's *t*-test was used to test for significant differences ($p \leq 0.05$) in the mean BOLD signal change between groups, over all the regions of interest in each task. *Post-hoc* independent Student's *t*-tests were also conducted to assess significant differences in a separate analysis between the groups in each ROI in each task (if significant in the ANOVA). Independent *t*-tests also identified significant differences in groups in measures of age and weight. All results are shown as the mean ± SEM.

6.2.6 Behavioral Measures

Response data were collected for the spatial attention task and the working memory task. Due to the nature of the verbal fluency task no behavioral measures were obtained. Reaction time (msec) was assessed for each condition in the working memory (arrow control condition and 5 digit condition) and spatial attention tasks (attended stimuli and unattended stimuli). A one-way analysis of variance (ANOVA) was used to assess between-group differences in the change in reaction time on the tasks and paired t-tests were applied to assess within-group differences in performance from baseline to post-treatment.

Independent t-tests also identified significant differences in groups in measures of age and weight.

6.3 Results

6.3.1 Subjects

Thirty-three subjects participated in the study. Twelve subjects (7 males, 5 females) received treatment with placebo, 12 subjects (10 males, 2 females) received treatment with valproate, 9 subjects (6 males, 3 females) received treatment with lithium. There were no significant differences between these groups in terms of age or weight (Table 6.1). Two subjects (one placebo, one valproate) did not complete both a pre- and post-dextroamphetamine scan due to technical difficulties. Therefore the spatial attention task and working memory task data was obtained in 11 subjects treated with valproate, 11 subjects treated with placebo and 9 subjects treated with lithium. Moreover, in the word generation task one additional subject treated with placebo failed to complete the task both at baseline and post-treatment, leaving only 10 subjects treated with placebo for further analysis. These subjects have been excluded from the analysis, as we could not assess the change due to treatment from baseline in these volunteers.

Table 6.1: Demographics for Treatment Groups; sex, age and weight.

Age equals mean years ± SEM, and weight equals mean weight in lbs ± SEM.

Treatment Group	Number of Subjects	Age	Weight
Placebo	12 (7 males)	25.8 ± 1.7	160.8 ± 8.8
Valproate	12 (10 males)	27.1 ± 1.8	166.7 ± 7.6
Lithium	9 (6 males)	25.8 ± 2.9	169.4 ± 7.6

6.3.2 Functional Imaging Measurements

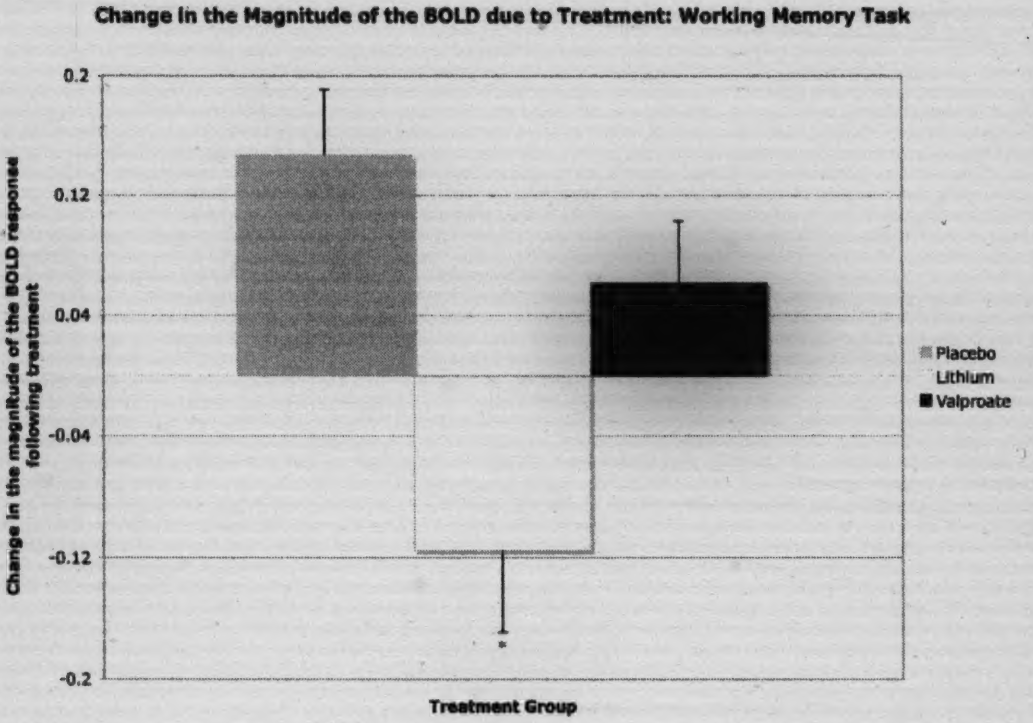
Working Memory Task:

There was a significant group effect in the analysis of the change in BOLD signal between the three treatment groups during the working memory task (F =8.246, df = 2, p < 0.000). *Post hoc* Bonferroni correction for multiple comparisons revealed a significant difference between the placebo and lithium groups (p < 0.000). Independent t-tests revealed that the lithium group had a significantly decreased change in BOLD signal from baseline to the second scan, compared to the placebo group (p < 0.000). There was no significant difference between the change in BOLD signal between the placebo and valproate groups (p = 0.599) (Figure 6.1).

Further *post hoc* independent t-test analysis to detect significant differences between the placebo and lithium groups in each ROI revealed that the lithium group had a significantly decreased change in BOLD signal in the right inferior parietal lobe (p = 0.008, the right precentral gyrus (p = 0.038) and approached significance in the left and right superior parietal lobe (p = 0.057 and p = 0.061, respectively) (Table 6.2).

Figure 6.1: Change in the magnitude of blood-oxygen-level-dependent (BOLD) signal across all regions of interest during performance of a working memory task in three treatment groups: placebo, lithium and valproate.

* equals p-value significant ≤ 0.05 level compared to the placebo group.

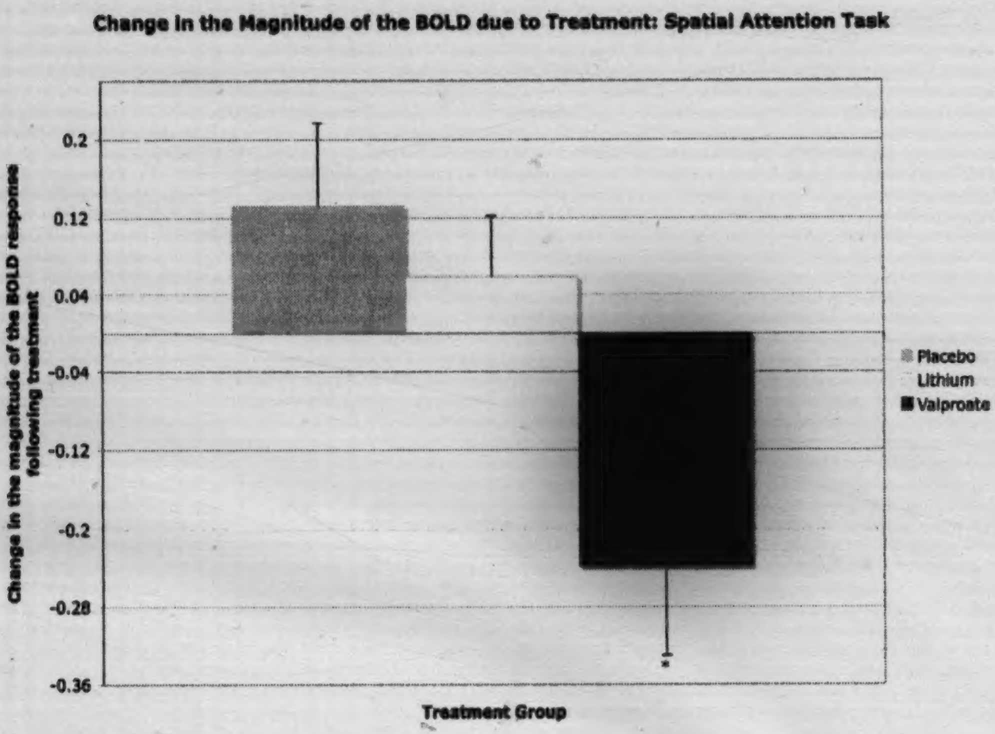


Spatial Attention Task:

There was a significant group difference in a one way ANOVA of the change in BOLD signal between the three treatment groups (F = 5.885, df = 2, p = 0.003). *Post hoc* Bonferroni correction for multiple comparisons revealed a significant difference between the valproate and placebo groups (p = 0.004). Independent t-tests showed that the valproate group had a significantly decreased change in BOLD signal from baseline to scan two, compared to the placebo group (p = 0.003). There was no significant difference between the lithium and placebo groups (Figure 6.2). Further *post hoc* independent t-test analysis of the separate ROIs showed that the valproate group had a significant decrease in BOLD signal in the left lingual gyrus (p=0.024) compared to the placebo group, from baseline to scan two (Table 6.2).

Figure 6.2: Change in the magnitude of blood-oxygen-level-dependent (BOLD) signal across all regions of interest during performance of a spatial attention task in three treatment groups: placebo, lithium and valproate.

*** equals p-value significant at ≤ 0.05 level compared to the placebo group.**



Word Generation Paradigm:

There was a significant difference between the groups in the change in BOLD signal during the verbal fluency task, assessed by ANOVA (F = 3.560, df = 2, p = 0.030). Because the groups possess an equal variance *post hoc* analysis using Bonferroni correction was applied to test the lithium vs. placebo groups and a Tamhane correction (because the groups possess unequal variance) was applied to test the valproate vs. placebo groups. These corrections revealed a significant difference between the valproate and placebo groups (p = 0.050), and a value that approached significance for the lithium and placebo groups (p = 0.061) (Figure 6.3). Independent t-tests revealed a significant decrease over the two scans in the change in BOLD signal for the lithium and valproate groups, compared to the placebo group (p = 0.011; p = 0.017). Further *post hoc* independent t-test analysis of the separate ROIs showed that the lithium group had a significant decrease in BOLD magnitiude in the right inferior parietal gyrus (p = 0.038) and the right superior parietal gyrus (p=0.008) and that the valproate group had a significant decrease in BOLD magnitude in the supplementary motor areas (p = 0.043), compared to the placebo group (Table 6.2).

Figure 6.3: Change in the magnitude of blood-oxygen-level-dependent (BOLD) signal across all regions of interest during performance of a word generation task in three treatment groups: placebo, lithium and valproate.

* equals p-value significant at ≤ 0.05 level compared to the placebo group.

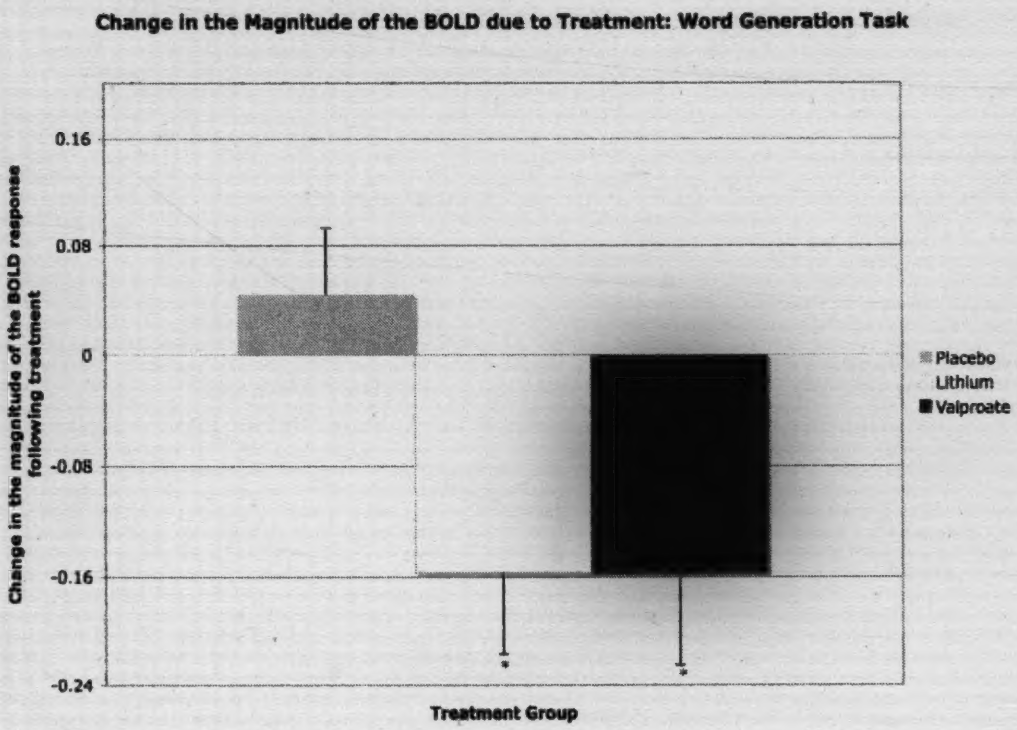


Table 6.2: Mean change values for magnitude of BOLD signal

This table contains the mean blood-oxygen-level-dependent (BOLD) values for each task overall, and (if statistically significant) it shows the pre-defined regions of interest in which *additional* analysis showed either a statistically significantly difference (p ≤0.05) on independent *t*–test between treatment groups, or a trend towards statistical significance. ROIs for tasks: **working memory task**: right insula (RINS), left inferior parietal gyrus (LIP), right inferior parietal gyrus (RIP), left superior parietal gyrus (LSP), right superior parietal gyrus (RSP), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIF), left middle frontal gyrus (LMF), right middle frontal gyrus (RMF), left superior frontal gyrus (LSF), right superior frontal gyrus (RSF), left inferior occipital gyrus (LIOG), right inferior occipital gyrus (RIOG), left precentral gyrus (LPCG), right precentral gyrus (RPCG), left insula (LINS) and cingulate gyrus (CING); **spatial attention task**: cuneus (CUN), left middle occipital gyrus (LMOG), right middle occipital gyrus (RMOG), left lingual gyrus (LLG), right lingual gyrus (RLG), right superior parietal gyrus (RSP), precuneus (PRECUN), left superior parietal gyrus (LSP), right middle occipital gyrus (RMOG); **word generation paradigm**: left inferior parietal gyrus (LIP), left superior parietal gyrus (LSP), right inferior parietal gyrus (RIP), right superior parietal gyrus (RSP), broca's area (BRO), left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), left precentral gyrus (LPCG), right precentral gyrus (RPCG), cingulate gyrus (CING), supplementary motor area (SMA), left superior temporal gyrus (LST), right superior temporal gyrus (RST), thalamus (THA).

	ROI	Placebo Group (mean value ± SEM)	Lithium Group (mean value ± SEM)	Valproate Group (mean value ± SEM)	p-value
Memory					
Mean change BOLD magnitude		0.15 ± 0.04	- 0.12 ± 0.05	0.06 ± 0.04	0.000*
	RIP	0.59 ± 0.19	-0.15 ± 0.13		0.008*
	RPCG	0.37 ± 0.16	-0.15 ± 0.16		0.038*
	LSP	0.26 ± 0.19	-0.22 ± 0.13		0.057
	RSP	0.47 ± 0.18	-0.08 ± 0.19		0.061
Spatial Attention					
Mean change BOLD magnitude		0.13 ± 0.08	0.06 ± 0.06	-0.24 ± 0.09	0.003**
	LLG	0.59 ± 0.21		-0.20 ± 0.22	0.024**
Verbal					
Mean change BOLD magnitude		0.04 ± 0.05	-0.16 ± 0.06	-0.16 ± 0.07	0.011* / 0.017 **
	RIP	0.14 + 0.12	-0.41 + 0.20		0.038*
	RSP	0.25 + 0.10	-0.44 + 0.18		0.008*
	SMA	0.18 + 0.20		-0.64 + 0.30	0.043**

*** placebo vs. lithium (p ≤ 0.05)**

**** placebo vs. valproate (p ≤ 0.05)**

6.3.3 Behavioral Measures

There were no significant differences in ANOVA assessment of ***the change in reaction times*** from before to after treatment across the three treatment groups in either the working memory or spatial attention tasks (*working memory task*; arrow condition F= 2.268, p = 0.122; 5- digit condition F = 2.255, p = 0.124; *spatial attention task*; attended condition F=0.804, p = 0.458; unattended condition F = 1.159, p = 0.329).

In the working memory task, reaction time data were available for eleven subjects who received treatment with placebo. There was a significantly decreased reaction time during the arrow condition in the second scan, compared to the first (p = 0.012). There was also a trend towards significant improvement in reaction time during the 5 digit condition (p = 0.070) (Table 6.3). In the spatial attention task, reaction time data were available for ten subjects treated with placebo. Reaction times were significantly decreased in both the attended and unattended conditions for this task (p = 0.008; p = 0.014) at the second scan (Table 6.4).

Reaction time for nine subjects treated with lithium was available in the working memory task. Both in the arrow and the 5-digit condition reaction times were decreased significantly during the second scan (p = 0.017; p = 0.028) (Table 6.3). In the spatial attention task, where data from eight subjects treated with lithium were available, there were no significant changes in reaction time from scan one to scan two (Table 6.4).

Lastly, data from the eleven subjects in the valproate group showed no significant differences between baseline and scan two in either performance measures during the working memory conditions or in the spatial attention conditions (Table 6.3; Table 6.4).

Table 6.3: Reaction time: Working Memory Task.

Values represent mean ± S.E. of rate of reaction (milliseconds).

	Time to reaction for arrow condition (msec)			**Time to reaction for 5- digit memory condition (msec)**		
	Placebo Group	Lithium Group	Valproate Group	Placebo Group	Lithium Group	Valproate Group
Baseline	523.58 ± 22.24	454.24 ± 17.32	348.95 ± 55.30	879.52 ± 25.14	913.18 + 62.13	800.21 ± 47.61
Post - treatment	480.77 ± 15.07	422.81 ± 22.73	371.84 ± 61.46	820.78 ± 40.09	818.00 + 53.79	851.19 ± 53.69
p-value	0.012 *	0.017 *	0.528	0.070	0.028 *	0.491

Table 6.4: Reaction time: Spatial Attention Task

Values represent mean ± S.E. of rate of reaction (milliseconds).

	Time to reaction for attended trial (msec)			**Time to reaction for unattended trial (msec)**		
	Placebo Group	Lithium Group	Valproate Group	Placebo Group	Lithium Group	Valproate Group
Baseline	317.70 ± 10.95	302.51 ± 15.54	285.62 ± 10.55	346.84 ± 12.83	313.68 ± 19.20	321.71 ± 14.07
Post - treatment	299.53 ± 11.89	291.42 ± 19.08	277.54 ± 11.81	328.84 ± 11.57	321.39 ± 18.44	283.81 ± 27.37
p-value	0.008 *	0.128	0.209	0.014 *	0.198	0.244

6.4 Discussion

The present study has shown a task-dependent change in regional brain activity following lithium and valproate treatment in healthy volunteers. A significant decrease in mean BOLD signal was observed during the working memory task after lithium treatment, but not in valproate-treated individuals compared to the placebo group. In the volunteers treated with valproate, a significantly decreased mean BOLD magnitude change was observed during the spatial attention task, compared to the placebo group. Both treatment groups had a significant decrease in BOLD signal during the word generation paradigm after treatment, compared to the placebo group.

Previously our research group has shown that lithium and valproate exert task- and region- dependent effects on dextroamphetamine-induced changes in brain activation (Bell et al., 2005). The current study demonstrates that lithium and valproate alone exert differential effects on brain activity in healthy control subjects.

The current study is the first to demonstrate functional brain activity changes between volunteers treated with lithium and valproate. Although few studies have examined the effects of lithium and valproate outside of clinical populations, these two drugs cause a range of cognitive impairments in healthy subjects. Deficits on the WAIS digit symbol subtest and Trails A test (Judd, 1979) as well as deficits in semantic processing, alertness, recall and memory have all been shown in lithium-treated healthy volunteers (Kropf and Muller-Oerlinghausen, 1979; Glue et al., 1987; Muller-Oerlinghausen et al., 1977;

Weingartner et al., 1985; Stip et al., 1999). Moreover, Stip et al. (2000) have shown that lithium administration, in healthy volunteers, delays or alters the pace of learning attention tasks. Similarly, Kropf and Muller-Oerlinghausen (1979) have observed a decrease in learning ability in healthy volunteers after 2-weeks of lithium treatment, on a recall task. Similar deficits in task learning have not been investigated after treatment with valproate. However, in healthy individuals treated with valproate, Meador and colleagues (2003) found that 3-17% of participants complained of cognitive deficits in the domains of memory, speech, concentration, and psychomotor slowing. Moreover, in an earlier study Meador et al. (1995) found deficits in healthy subjects treated for one month with valproate in a delayed memory recall test, a symbol digit modalities test and a visual serial addition test, compared to baseline. Previous studies have not compared or contrasted the cognitive impact of these two mood stabilizers; however a study by Stoll and colleagues (1996) in bipolar patients found that substitution of lithium with divalproex sodium was effective in reducing the cognitive side effects of lithium for these patients. Therefore, it is not clear to what extent lithium and valproate share cognitive dysregulations; it may be that the two drugs alter performance along different domains to different extents, lithium treatment presenting with greater impairment than valproate.

What we have observed in terms of performance on the cognitive tasks in treated healthy controls in the current study tells us several things. Firstly, we did not observe any significant differences between the treatment groups on the ***change*** in performance from baseline to post-treatment. This would seem to indicate that altered levels of performance across the treatment groups have not significantly impacted our current fMRI results, which have also focused on the change in signal from baseline to post-treatment. However, the performance data also demonstrate that the placebo group improved on both reaction time in the working memory (approaching significance) and spatial attention tasks at the second scan. We suggest that this improvement potentially reflects a practice effect. However, the lithium group only improved on the working memory task, while subjects treated with valproate showed no improvement on either task. It is important to note that in neither treatment group did we observe a decrease in performance at the second scan, which would seem to indicate that any treatment effect on performance, we hypothesize, affected only learning of the tasks.

The fact that valproate and lithium demonstrate differential effects on task-dependent regional brain activity suggests that while both drugs act as mood stabilizers each exerts unique influences on cognition and regional brain activity changes. This is particularly important in terms of functional imaging studies investigating patients suffering from bipolar disorder. Patients on treatment, in particular lithium, often suffer cognitive side effects (Joffe et al., 1988; Squire et al., 1980; Stoll et al., 1996; Kocsis et al., 1993; Pachet et al., 2003), and various studies have demonstrated cognitive deficits in bipolar patients (Martinez-Aran et al., 2004; Harmer et al., 2002; Adler et al., 2004; Tam et al., 2004; Marvel and Paradiso, 2004; Clark and Goodwin, 2004) as well as functional alterations during task performance (Caliguiri et al, 2003, Adler et al. 2004, Caliguiri et al., 2004, Elliot et al., 2004, Gruber et al., 2004, Lawrence et al., 2004, Malhi et al., 2004a, Malhi et al., 2004b, Monks et al., 2004). However, because most patients are medicated at the time of study, it is difficult to interpret to what extent treatment factors into these performance deficits. In a recent study we conducted, 2 weeks of lithium treatment in euthymic patients has also indicated that a treatment effect is present and can be detected using fMRI (unpublished data).

We acknowledge that one important factor that may limit the interpretation of the current results is the gender distribution of our sample. The three groups all contained fewer female subjects than male subjects. Some previous functional imaging studies suggest that males and females demonstrate altered regional brain activity across a variety of cognitive and emotional paradigms (Fischer et al., 2004; Lee et al., 2004; Weiss et al., 2003; Lee et al., 2002; Georgopoulos et al., 2001; Cowan et al., 2000; Ragland et al., 2000; Speck et al., 2000; Levin et al., 1998; Shaywitz et al., 1995). In the future, assessing only one gender is likely a better course of action to eliminate this potential confound. In fact, in our more recent patient fMRI research, we have concentrated on samples consisting of only one gender to eliminate the effects of sexual dimophisms both in regional brain activity and cognitive performance.

In conclusion, the present study shows that lithium and valproate both decrease BOLD signal magnitude, compared to placebo, although in varied tasks and regions. It is also likely that treatment is a contributing factor in the cognitive deficits and regional brain activity changes observed in bipolar patients undergoing pharmacotherapy.

(A version of this chapter has been published– see Bell et al., (2005) Human Psychopharmacol, 20: 415-424)

Unlike our hypothesis, which anticipated that we would not find significant differences in brain activity brought about by 14 days of treatment with lithium or valproate, we have observed that these two medications produce a range of task- and region- dependent effects, decreasing brain activation in healthy control. This highlights medication confounds which occur in functional neuroimaging studies in bipolar patients on medication.

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SECTION II

Chapter 7. Males and females differ in brain activation during cognitive tasks.

7.1 Introduction

It has long been recognized that males and females exhibit differential performance on various cognitive tasks, including tests of visual–spatial and verbal domains (Kimura, 1996 and Wegesin, 1998). Moreover, males and females experience different propensities for the development of neuropsychiatric disorders, may report different symptom profiles clinically, and present with altered levels of functioning and comorbidity (Kessing, 2004, Marneros et al., 2004, Winkler et al., 2004, Riecher-Rossler and Hafner, 2000, Weinstock, 1999 and Endicott, 1998). These differences may reflect innate functional brain differences between the genders.

Sexual dimorphism of cognitive ability has consistently been shown to occur in two domains; in tests of spatial ability (mental rotation and spatial perception) where men outperform women and in tests of verbal ability (particularly verbal fluency), where women outperform men (Wegesin, 1998). Thus, most studies suggest that females perform better than males in tasks of verbal fluency, manual speed (i.e. finger tapping), and verbal and item memory, while males perform better than females in visuospatial tasks such as mental rotation, spatial rotation, and mathematical tasks (for full review see Kimura, 1996).

Previously, functional asymmetries in cerebral organization between males and females have been observed using PET and SPECT in the study of cerebral metabolic rate and resting state CBF, respectively (Li et al., 2004, Kastrup et al., 1999, Gur et al., 1995, Gur and Gur, 1990 and Rodriguez et al., 1988). In general, this research seems to suggest that females have a higher regional CBF than males (Kastrup et al., 1999). More recently, functional imaging studies, including fMRI studies, have been conducted to investigate gender influence upon regional brain activity changes and regional CBF changes occurring during stimulus presentation. Tasks of mental rotation, visual stimulation, emotional recognition, verbal processing, and object construction have all shown significant patterns of differential activation between the sexes (Fischer et al., 2004, Lee et al., 2002, Lee et al., 2005, Weiss et al., 2003, Georgopoulos et al., 2001, Cowan et al., 2000, Ragland et al., 2000, Speck et al., 2000, Levin et al., 1998 and Shaywitz et al., 1995). Gender-specific alterations in brain activation have been observed (across the various paradigms) in insular and thalamic regions (Lee et al., 2002 and Lee et al., 2005), occipital and cingulate regions (Fischer et al., 2004 and Lee et al., 2002), frontal regions (Lee et al., 2002), parietal regions (Weiss et al., 2003), and temporal regions (Ragland et al., 2000), as well as altered lateralization between the hemispheres (Lee et al., 2002, Georgopoulos et al., 2001, Speck et al., 2000, Levin et al., 1998 and Shaywitz et al., 1995). Despite the general consensus that suggests differences between males and females, not all studies have found a significant gender effect (Schlosser et al., 1998). Excluding those fMRI studies which have employed emotional paradigm challenges (for which results are dependent on several factors including the emotion induced, the modality of the paradigm as well as gender specifics of the induced emotion), other studies suggest that females have greater bilateral activation during a phonological language task (Shaywitz et al., 1995), and greater lateralization to the left hemisphere during a working memory task (Speck et al., 2000). Additionally, females have demonstrated more frontal activation, compared to more parietal activation in males, during a mental rotation task (Weiss et al., 2003), and males have demonstrated a greater bias towards right hemisphere activation (and females to left hemisphere activation) during a task requiring a judgement of a whole object from its parts (Georgopoulos et al., 2001). Finally, females have also demonstrated a greater bilateral regional cerebral blood flow in temporal regions during performance of the Wechsler Memory Scale for memory recall (Ragland et al., 2000).

While some of the cognitive paradigms have demonstrated gender biases in terms of performance (females perform more accurately (although slower) on working memory task (Speck et al., 2000)) and on memory recall (Ragland et al., 2000), others have not (verbal test of orthographic, semantic, and phonological processing; Shaywitz et al., 1995; visuospatial test of mental rotation; Weiss et al., 2003).

The idea of teasing out gender effects in brain activation is difficult when we know that previous neuropsychological evidence supports gender-specific performance abilities in males and females on a variety of cognitive domains. For this reason, it is important to try and understand the possible relationships between gender, cognitive performance, and brain activation. In fact, findings from a recent study by Unterrainer et al. (2005) have shown both sex-specific and individual task performance-specific influences upon regional brain activity during a planning task.

Using the BOLD response, we have assessed differences in regional brain activation in a group of male and female healthy volunteers over a variety of cognitive domains; verbal fluency, spatial attention, working memory, and motor tasks. Our hypotheses were first, that males and females would differ in brain activation patterns during spatial attention (for which males outperform females) and during verbal fluency (where females outperform males) but not necessarily during a motor task or in working memory performance where neuropsychological data do not support sexual dimorphism. In conjunction with this, we hypothesized that gender differences in cognitive performance on the tasks would be reflected by gender differences in the same direction on measures of brain activation. Thus, females would demonstrate a greater activation during the verbal task; males during the spatial attention task and both genders would show equivalent brain activity during the motor tasks. We did not make any hypothesis regarding the direction that either findings of performance or brain activation during the working memory task might take, although Speck et al. (2000) have demonstrated increased left hemisphere lateralization in females in this domain.

7.2 Methods

The ethics board of the University of Alberta Hospital approved this study.

7.2.1. Subjects

Thirty-three right-handed healthy volunteers (23 males, 10 females) were recruited through poster advertising from the university community. Subjects underwent a medical exam and medical history, and a detailed semi-structured clinical interview (structured clinical interview for DSM-IV) to rule out past or present psychiatric illness. Past and present drug and alcohol use was assessed and subjects were excluded based on current abuse of these substances. Subjects who had used recreational drugs in the past 6 months, or amphetamine in the past year were excluded from participating.

7.2.2 Tasks

The tasks are those we have used and described in previous research studies (Willson et al., 2004 and Bell et al., 2005). All tasks were blocked design; the working memory task was composed of seven 24 sec blocks of each control (arrow condition) and test condition (5-digit memory condition); the spatial attention task was composed of 10 blocks of each control (attended stimuli) and test (unattended condition) of 24 sec duration; the word generation task was composed of five 40-sec blocks of each control (pseudo REST condition) and test (word generation) conditions; the motor tasks were composed of four blocks of on and off finger tapping each for 40 sec.

Working memory task

The working memory task consisted of two conditions. In the first condition, there was a series of 10 arrows pointing to the left or to the right. Subjects responded by pressing the left or right button. In the second condition, a five-digit number was displayed for 4 sec with the instruction 'Remember this Number'. Immediately after, a series of 10 random single digits was presented. Subjects were asked to respond by pressing one button for yes and one for no if the single digit was or was not in the memorized number. In all, each condition was presented seven times in 24 sec blocks pseudo-randomly arranged.

Spatial attention task

For this task, subjects were asked to respond as quickly as possible to certain criteria. First, a black cross appeared on the screen. Soon after, the black cross would appear with the target (a black square). Whenever the black cross and square appeared together, subjects responded by pressing the button in their dominant hand as fast as possible. The delay between the appearance of the cross and the target was varied randomly from 300 to 1100 msec. Approximately 10% of the trials were actually catch trials designed to ensure that subjects were engaged in the task. In a catch trial, another black cross appeared instead of the target and subjects were instructed not to respond. Any responses to catch trials were considered errors, and the error rate could therefore be measured. In this experiment, two conditions of the reaction task were alternated to maintain spatial attention (Beauchamp et al., 2001 and Cabeza and Kingstone, 2001). In the first condition, the cross and square appeared in the same location (attended location), and in the second condition, the target appeared a distance away from the cross (unattended). There is significant evidence to suggest that spatial attention, such is needed to do this task, is analogous to a "mental spotlight" that requires a certain connectivity to operate properly (Willson et al., 2004). This task was performed in 10 alternating blocks of each condition, 24 sec in duration each.

Word generation paradigm

The verbal task utilized a word generation paradigm in which there were two conditions. In the first condition, subjects were asked to repeat the word 'REST' silently until another instruction was given. In the second condition, a series of 10 single letters randomly chosen from the alphabet was displayed at 4-sec intervals. During the display of a single letter, subjects responded by thinking of as many words as possible that begin with that letter and repeating them silently until another letter is presented or the 'REST' instruction appears. The experiment consisted of five 40-sec blocks of each condition beginning with 'REST'.

Motor task

The motor task involved rapidly tapping the index finger. Subjects were instructed to "tap the index finger of the (given hand) as fast as you can comfortably while maintaining a steady pace". Instructions for the "Rest" and "Tapping" condition were given by a visual signal. Each condition (Rest or Tapping) was performed in four alternating blocks each lasting 40 s. This experiment was done twice, once with the left hand and then again with the right hand.

The four tasks were administered in a fixed manner starting with the motor tasks followed by the memory task, the spatial attention task, and finally the word generation task.

7.2.3 Behavioral Measurements

Response data were collected for the spatial attention task, the working memory task, and motor tasks. Due to the nature of the verbal fluency task, no behavioral measures were obtained. Reaction time (msec) was assessed for each condition in the working memory (arrow control condition and 5 digit condition) and spatial attention tasks (attended stimuli and unattended stimuli) and the average tapping rate (Hz) was assessed during finger tapping (left and right hand). Student's independent *t* test was used to assess between-group differences in the reaction times at baseline and to assess between-group differences on the spatial attention and working memory task errors.

7.2.4 Image Acquisition

The fMRI study was conducted on a 1.5-T Siemens Sonata scanner (Siemens, Erlangen, Germany) with a single shot eco-planar image (EPI) gradient echo sequence (TR = 4010 ms, TE = 50 ms, 1.7 × 1.7 mm, 4 mm thick) to acquire 30 contiguous slices obtained at an oblique angle along the AC–PC line. A high-resolution T1-weighted magnetization prepared rapid gradient echo sequence was also acquired during the imaging session to overlay the functional analysis (Willson et al., 2004).

7.2.5 fMRI Data Analysis

fMRI data analysis were conducted according to previously published methods (Willson et al., 2004 and Bell et al., 2005). Preprocessing and analysis were performed using Statistical Parametric Mapping (SPM99), 1999 version (SPM99–Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during preprocessing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. Sessions with realignment parameters of greater than 4 mm in the direction of translation (along the *x*, *y*, *z* axes) were excluded from the final statistical analysis, as were sessions with motion greater than 0.05 radians in a rotational plane (pitch, roll, yaw). The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 × 8 × 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2*-weighted EPI functional images. After normalization, all volumes were resampled to 2 × 2 × 2 mm voxels using trilinear interpolation in space. Finally, all functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between subject variability and allow Gaussian random field theory to give corrected statistical inferences (Friston et al., 1994). Initial analysis was performed separately for each subject for each task. The model specified for each task was kept identical for all subjects and sessions to create identical design matrices. As part of this analysis, three more preprocessing steps were performed using SPM99. First, the data were high pass filtered to remove low-frequency drifts in the signal. In addition, the data were low pass filtered using the hemodynamic response function to remove high-frequency noise. Effects due to global intensity fluctuations were removed when the data were proportionally scaled to a global mean of 100. The time series for each data set was analyzed according to the general linear model. Previously, we have performed a group analysis on 18 of these volunteers (5 females, 13 males) (Willson et al., 2004) by constructing a fixed effects model for each task. ROIs for each task were then compiled based on those anatomical areas which were activated to meet a threshold of P (corrected) of less than 0.05 and a cluster size of 10 voxels or more. These *most significantly activated voxels* from the group average generation maps were used to localize activation anatomically and the ROI images were constructed using AAL software (Tzourio-Mazoyer et al., 2002), running with MRIcro software (Rorden and Brett, 2000). These ROIs have been assessed in the current study. Regions of interest for tasks: *working memory task*: right insula, left inferior parietal gyrus, right inferior parietal gyrus, left superior parietal gyrus, right superior parietal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, left inferior frontal gyrus, right inferior frontal gyrus, left middle frontal gyrus, right middle frontal gyrus, left superior frontal gyrus, right superior frontal gyrus, left inferior occipital gyrus, right inferior occipital gyrus, left precentral gyrus, right precentral gyrus, left insula and cingulate gyrus; *spatial attention task*: cuneus, left middle occipital gyrus, right middle occipital gyrus, left lingual gyrus, right lingual gyrus, right superior parietal gyrus, precuneus, left superior parietal gyrus, right middle occipital gyrus; *word generation paradigm*: left inferior parietal gyrus, left superior parietal gyrus, right inferior parietal gyrus, right superior parietal gyrus, broca's area, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, left precentral gyrus, right precentral gyrus, cingulate gyrus, supplementary motor area, left superior temporal gyrus, right superior temporal gyrus, thalamus; *motor task*: left primary motor cortex, right primary motor cortex, supplementary motor area, left superior temporal gyrus, right superior temporal gyrus, left inferior parietal gyrus, right inferior parietal gyrus, left inferior frontal gyrus and right inferior frontal gyrus.

For each subject, the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels and BOLD signal magnitude within each ROI. In each individual activation map, for each task, a SVC was applied to compute the activation within each ROI. We have used a SVC because we previously have defined areas of activation (ROIs) in the statistical parametric map according to the results the 18 subject, fixed-effects analysis. Applying the SVC allows the choice of appropriate thresholds, given that we are confining our analysis to ROIs of defined shape and size. We have used a corrected *P* value threshold of 0.05 in the evaluation of the number of activated pixels in each ROI. The number of activated pixels in each ROI was counted for each subject in each ROI, in each task.

For each subject, the individual activation maps generated during single-subject analysis were used to identify the change in BOLD signal magnitude. The BOLD signal intensity change was calculated based on regions of interest using the MARSBAR toolbox for SPM (Brett et al., 2002) over a seven-voxel sphere centered on the *most* significantly active voxel in each ROI. The fitted response (or BOLD signal intensity change) is expressed in percentage of whole brain mean. Because the global brain mean in the voxel-wise analysis was scaled to 100, this signal change represents the percentage of signal change with respect to the global mean intensity of the scaled images. The number of voxels over which the fitted response was calculated was kept small in order to minimize averaging over non-significant voxels or large veins (Mulderink et al., 2002). Subsequently, statistical calculations for BOLD signal magnitude were based on the average response calculated from the plateau portion of the hemodynamic response (8 s after stimulus origination until stimulus termination) (Willson et al., 2004).

The mean number of pixels activated across all ROIs for all female and male subjects was calculated as well as the mean BOLD signal magnitude across all ROIs for all female and male subjects. Independent Student's *t* test was used to determine differences between the two groups (significance level of $p \leq 0.05$). If this was significant, *additional* independent Student's *t* tests were used to assess each ROI for differences between males and females in the task. For the motor tasks, a two-way ANOVA full factorial design was applied to test for the main effects of gender and hand of task as well as for an interaction effect.

7.3 Results

Thirty-three subjects participated in the study. There were no significant differences between these groups in terms of age (mean age ± SEM; males 26.7 ± 1.5, females 25.2 ± 2.0). One male subject failed to complete the baseline word generation paradigm. This subject was excluded from the analysis for this task.

7.3.1 Behavioral Performance

Working memory task

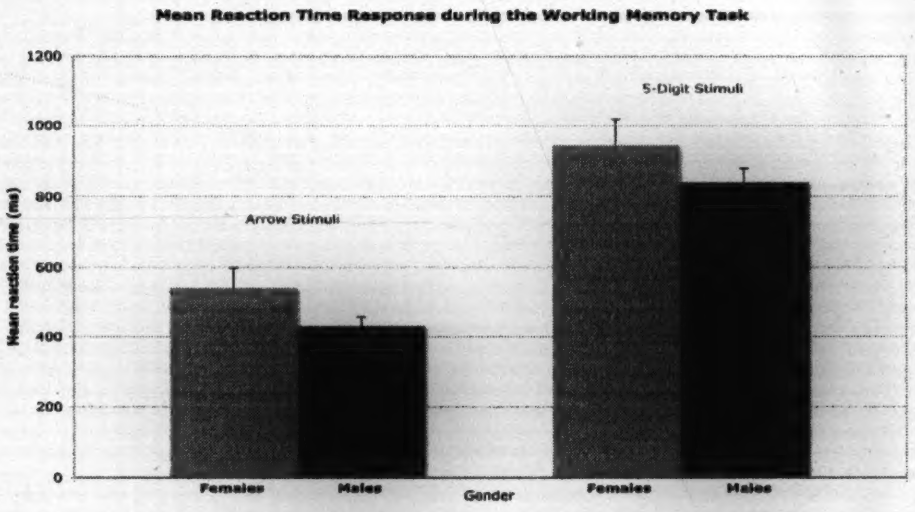
There were no significant differences in reaction time during the control or test conditions between males or females in the working memory task. In the control (arrow) condition, males had a reaction time of 430.28 ± 27.0 and females performed at 541.80 ± 57.7 ($p = 0.081$). During the memory condition, males performed with a reaction time of 841.22 ± 38.2 and females with a reaction time of 944.88 ± 74.1 ($p = 0.235$) (see Fig. 7.1a). There was no significant difference between males and females on errors in the task (males, 2.56 ± 2.06; females, 1.80 ± 1.64, $p = 0.41$).

Spatial attention task

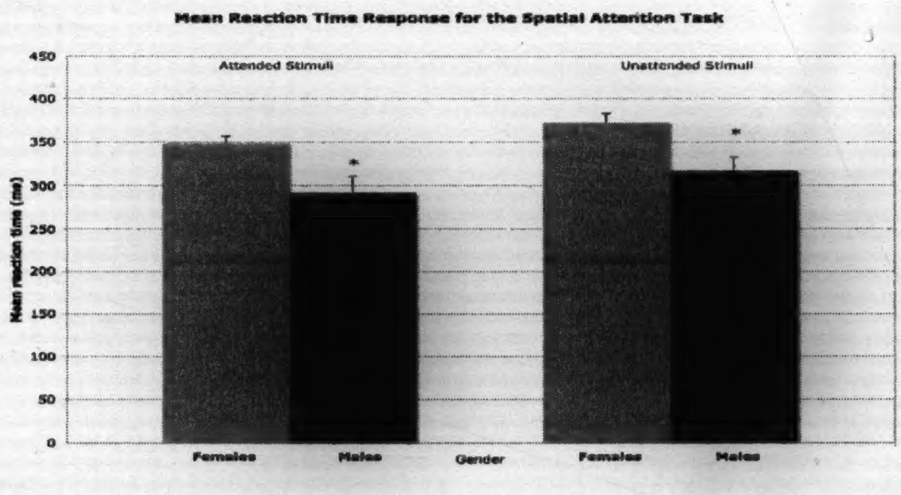
There was a significant difference in performance during both the control (attended) and test (unattended) conditions in males and females. The male subjects had significantly faster reaction times than the females in the attended condition (males 291.9 ± 8.2, females 348.5 ± 19.0; *p* = 0.004) and during the unattended condition (males 316.8 ± 10.2, females 372.7 ± 16.1, p = 0.006) (see Fig. 7.1b). The number of errors made during the catch trials was not significantly different in males and females (males, 4.17 ± 2.43; females, 2.63 ± 1.69, *p* = 0.118).

Figure 7.1: Mean reaction time (ms) of response for females and males during the two conditions in A) working memory task and B) spatial attention task. * indicates significance at $p \leq 0.05$.

A.



B.



Motor tasks

There were no significant differences between males and females in the performance of either the right or left finger tapping task, measured by the mean tapping frequency ($p = 0.964$ and $p = 0.313$, respectively). The mean tapping frequency for males was 2.98 Hz with the right hand and 2.43 Hz with the left hand. The mean tapping frequency for females was 3.00 Hz with the right hand and 2.80 Hz with the left hand.

7.3.2 fMRI Results

Working memory task

Independent *t* test demonstrated that males had significantly higher mean number of pixels activated ($p = 0.003$; Fig. 7.2a) and a greater mean BOLD signal magnitude ($p = 0.012$; Fig. 7.3a) than females in the working memory task. *Additional* analysis demonstrated that males had a greater number of pixels activated in the right superior parietal gyrus and the right inferior occipital gyrus, and a greater BOLD signal magnitude in the left inferior parietal gyrus (Table 7.1).

Spatial attention task

There was no significant difference between groups on the mean of the number of activated pixels or the mean BOLD magnitude ($p = 0.660$; Fig. 2b and $p = 0.924$; Fig. 7.3b) (Table 7.1).

Word generation paradigm

Males had a significantly larger mean number of pixels activated than females ($p = 0.005$; Fig. 7.2c) and a significantly greater BOLD magnitude than females ($p= 0.000$; Fig. 7.3c). *Additional* analysis of the individual ROI in this task showed no significant differences between males and females in the number of pixels activated, but did show greater mean BOLD magnitude in males in the right dorsolateral prefrontal cortex, the right inferior parietal gyrus (Table 7.1).

Motor task

A two-way ANOVA revealed no main effect of gender or hand of task performance for the number of activated pixels (gender effect $p = 0.762$, hand effect p= 0.811) or the BOLD magnitude (gender effect p= 0.133, hand effect p= 0.776). There was also no significant interaction effect between gender and hand of task performance for either fMRI measure ($p = 0.089$, $p = 0.242$, respectively).

Left hand

There were no significant differences between males and females on either the number of activated pixels of BOLD signal magnitude specifically noted in any of the regions of interest during performance on the left finger tapping task (Fig. 7.2 and Fig. 7.3) (Table 7.1).

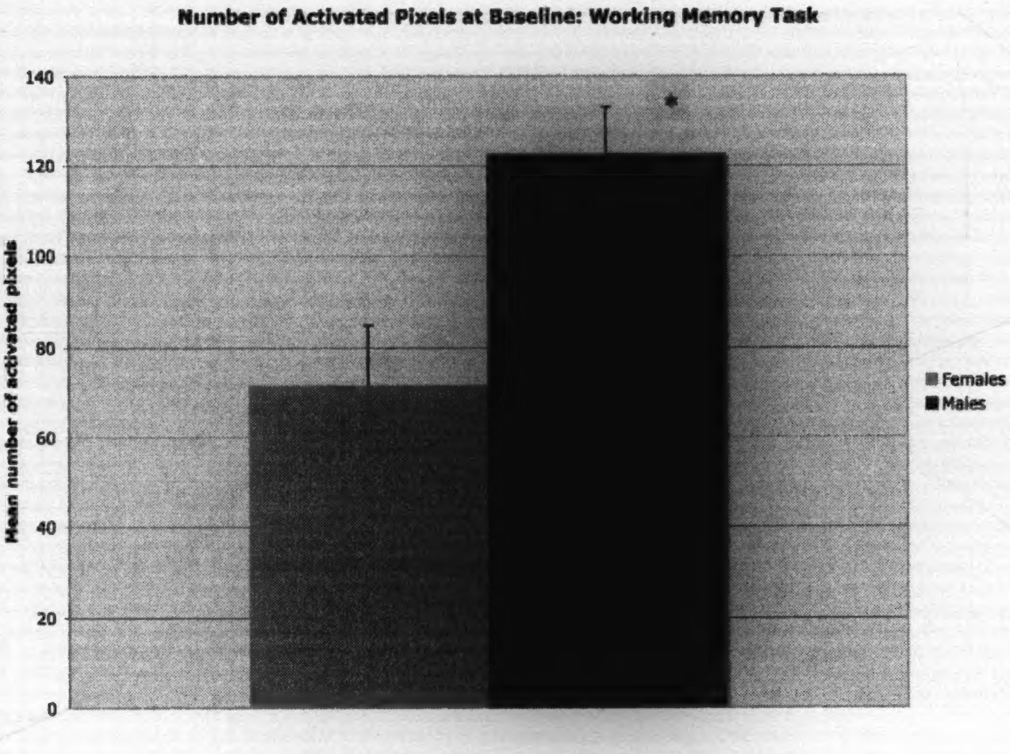
Right hand

Males had a significantly greater mean BOLD magnitude than females during performance of the right hand finger tapping task ($p = 0.053$). However, there were no significant differences between the two genders in terms of the number of activated pixels in this task ($p = 0.178$). Additional *t* tests demonstrated that males had a significantly larger BOLD signal magnitude in the right inferior parietal gyrus ($p = 0.029$) and left inferior frontal gyrus ($p = 0.013$) as well as a significantly larger amount of pixels activated in the left superior temporal gyrus ($p = 0.036$) (Table 7.1, Fig. 7.2 and Fig. 7.3).

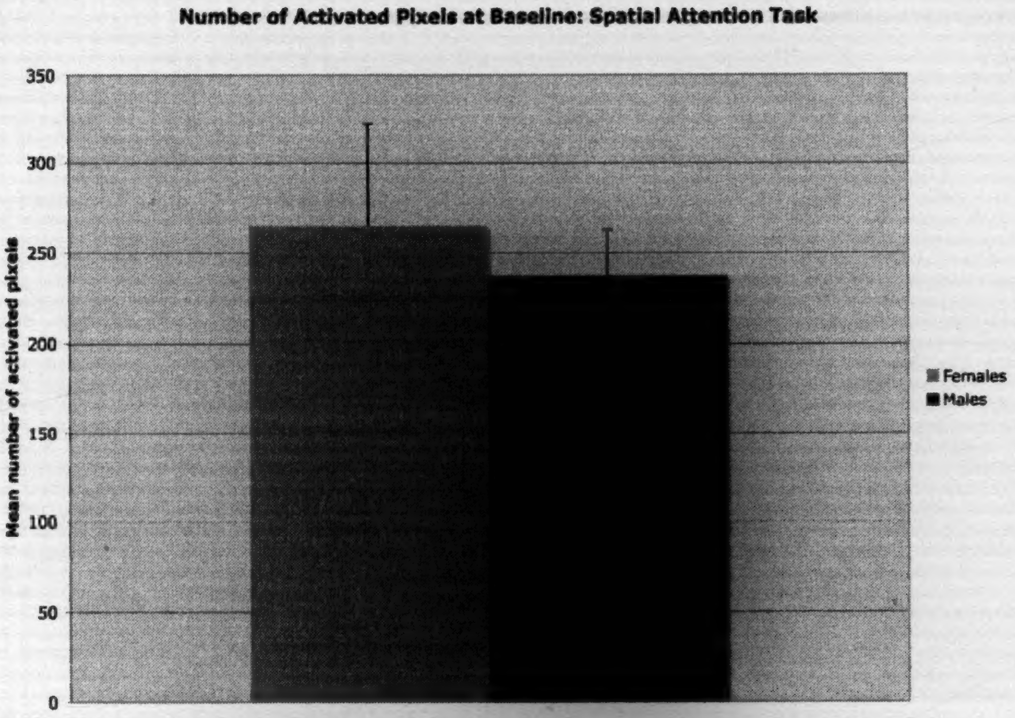
Figure 7.2: Mean number of activated pixels across regions of interest for A) working memory task, B) spatial attention task, C) word generation paradigm, D) motor task (left hand), and E) motor task (right hand), in males and females.

* indicates a p value significance of ≤ 0.05.

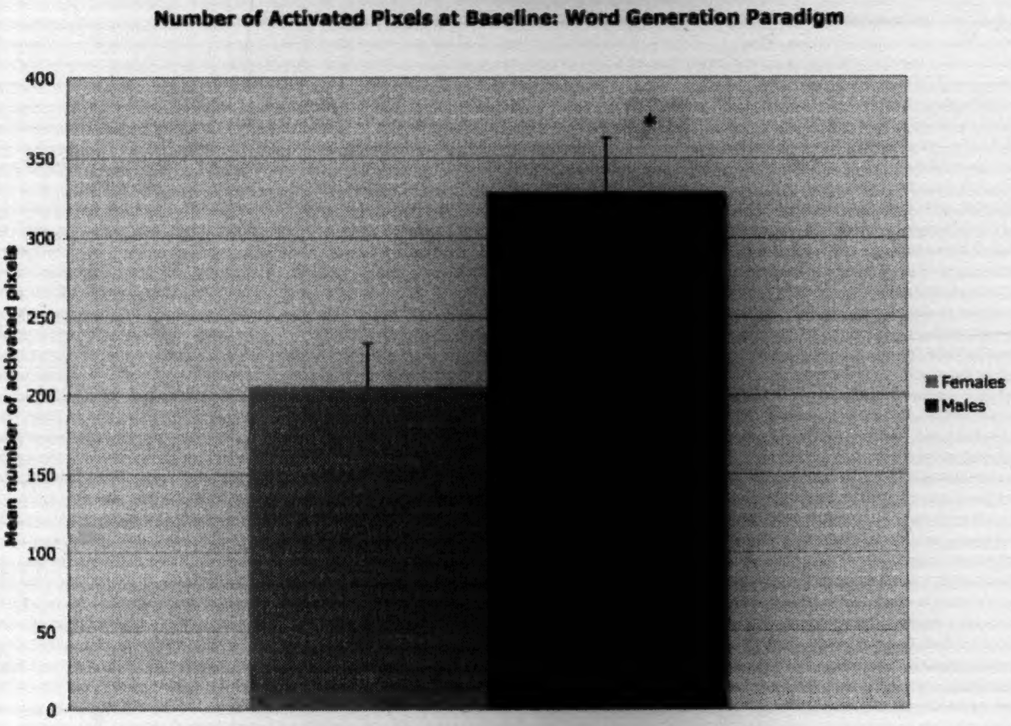
A.



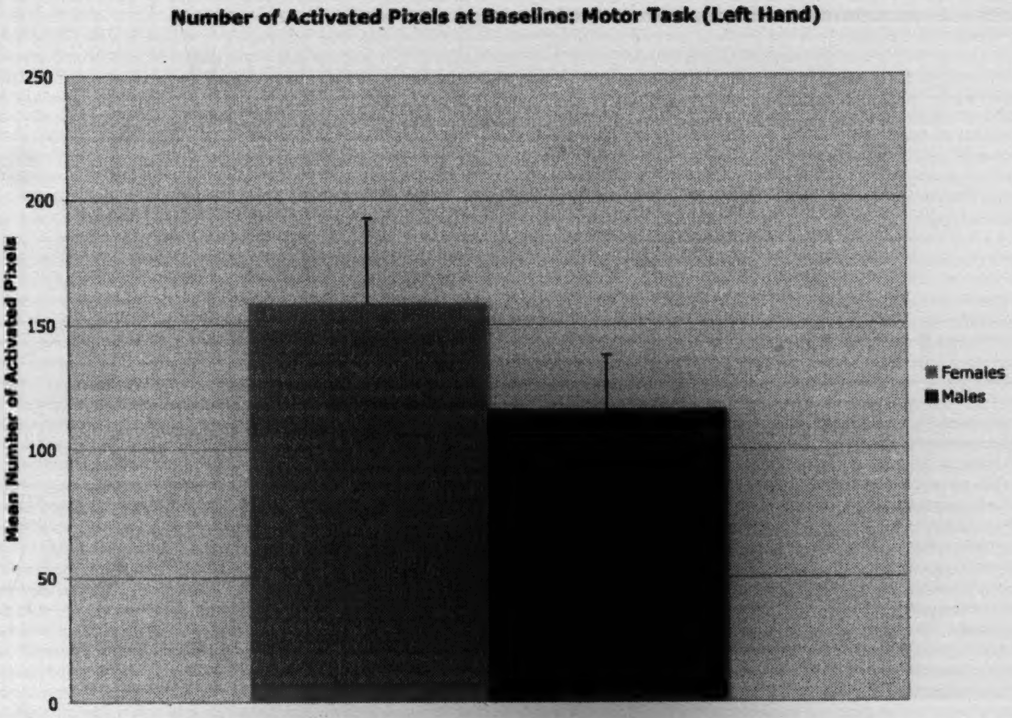
B.


Number of Activated Pixels at Baseline: Spatial Attention Task

C


Number of Activated Pixels at Baseline: Word Generation Paradigm

D.


Number of Activated Pixels at Baseline: Motor Task (Left Hand)
Mean Number of Activated Pixels
250
200
150
100
50
0
▨ Females
■ Males

E.

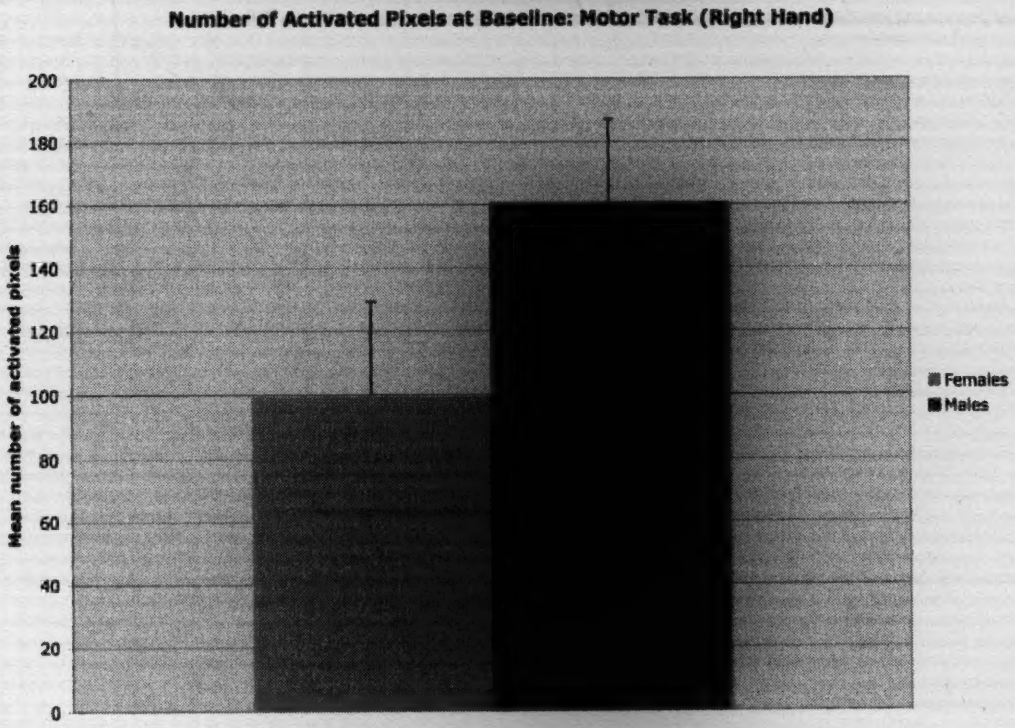
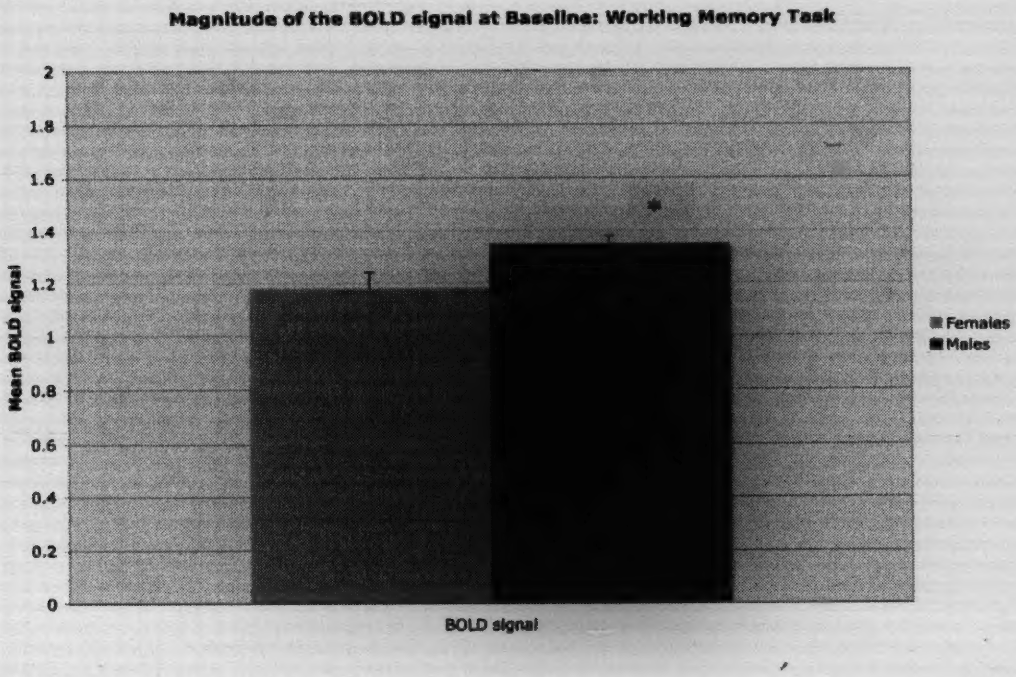

Number of Activated Pixels at Baseline: Motor Task (Right Hand)
Mean number of activated pixels
200
180
160
140
120
100
80
60
40
20
0
▨ Females
■ Males

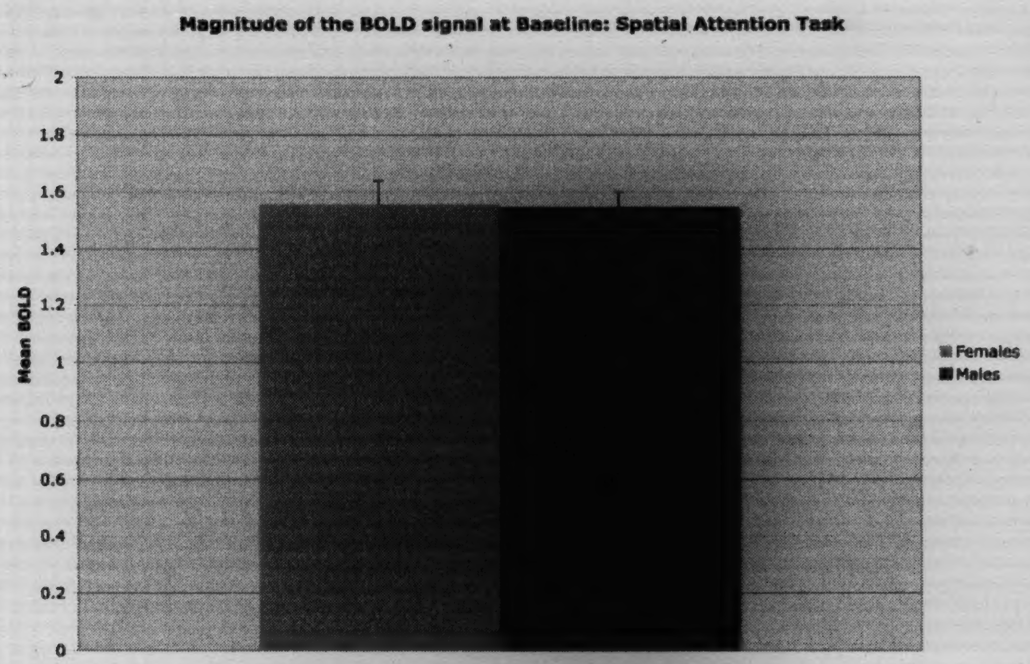
Figure 7.3: Mean magnitude of the BOLD signal across the regions of interest of A) working memory task, B) spatial attention task, C) word generation paradigm, D) motor task (left hand) E) motor task (right hand), in females and males.

Where * indicates a p-value significance of ≤ 0.05.

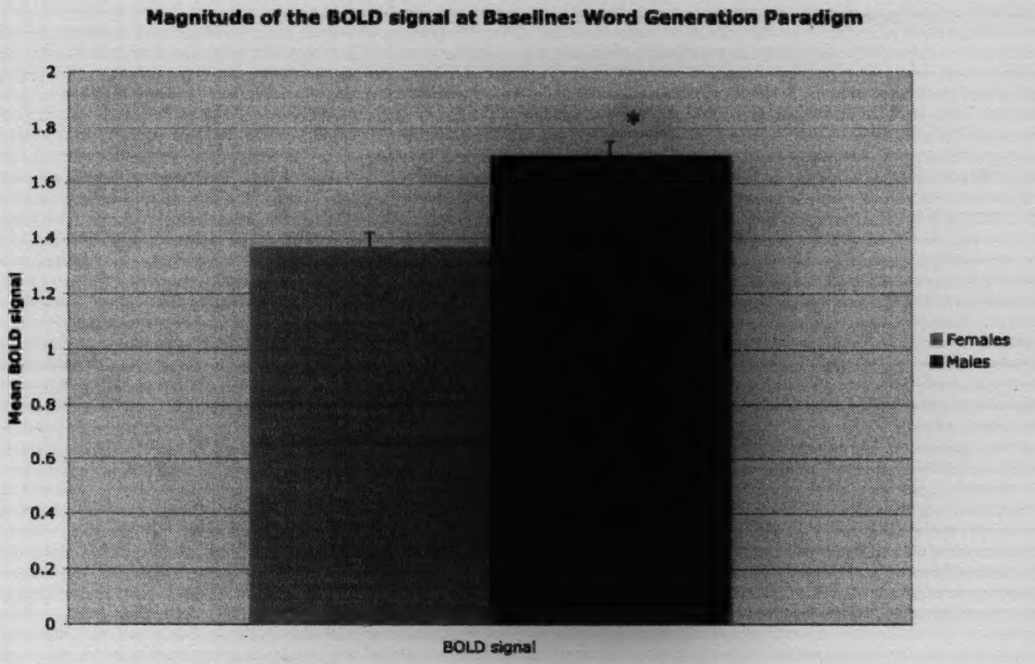
A.



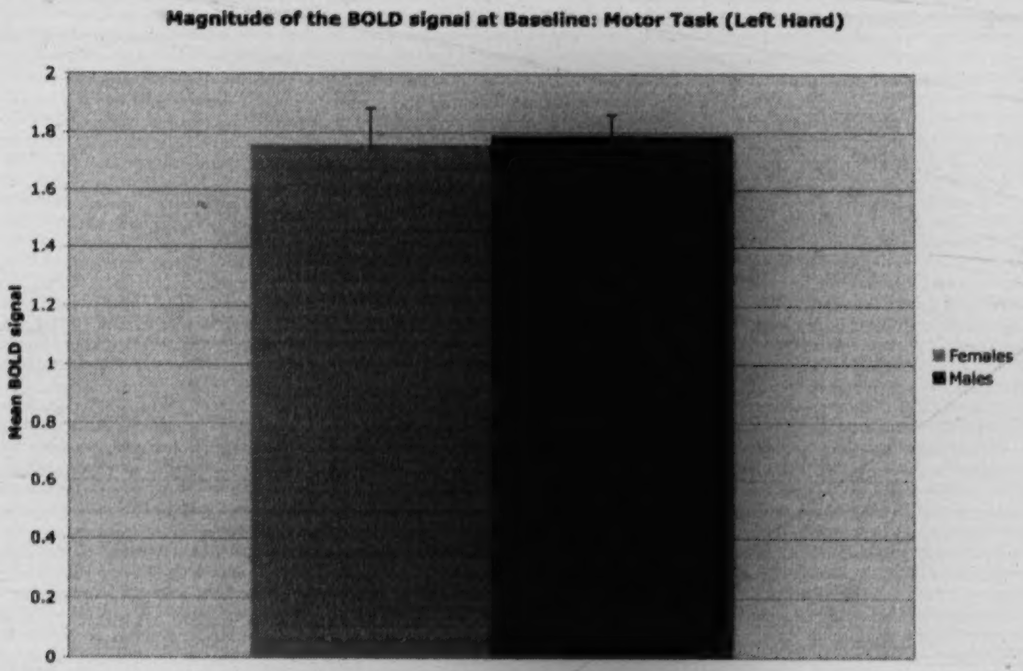
B.


Magnitude of the BOLD signal at Baseline: Spatial Attention Task
Mean BOLD
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
■ Females
■ Males

C.

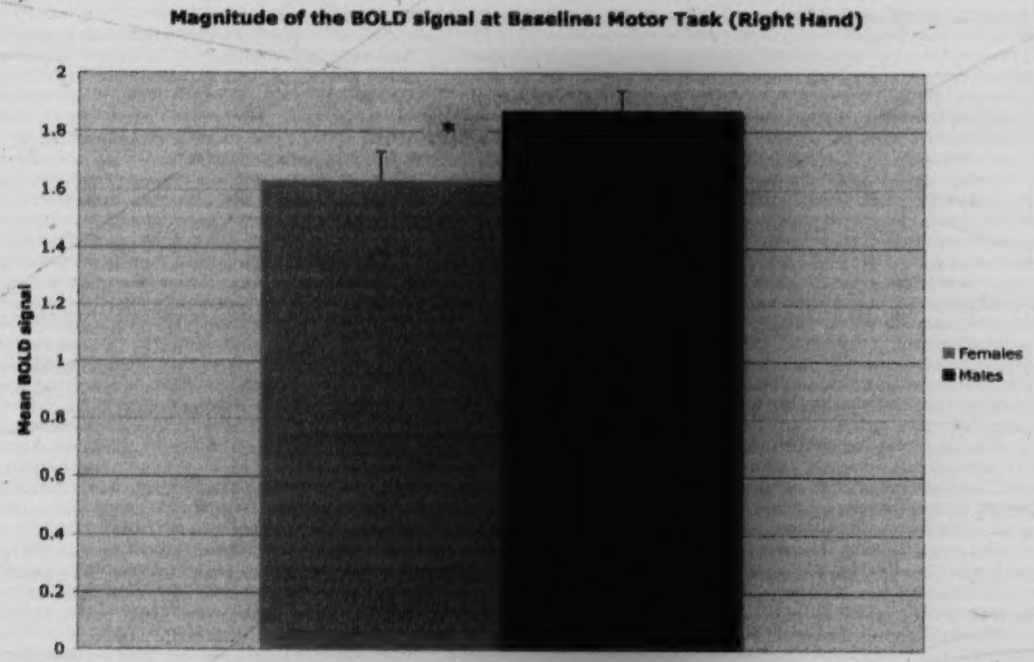

Magnitude of the BOLD signal at Baseline: Word Generation Paradigm
Mean BOLD signal
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
BOLD signal
■ Females
■ Males

D.



Magnitude of the BOLD signal at Baseline: Motor Task (Left Hand)
Mean BOLD signal
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
▨ Females
■ Males

E..



Magnitude of the BOLD signal at Baseline: Motor Task (Right Hand)
Mean BOLD signal
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
*
▨ Females
■ Males

Table 7.1: Mean value for the number of activated pixels and/or BOLD signal in post hoc analysis when significant ($p \leq 0.05$), or trend to significance, in regions of interest (ROI).

	ROI[a]	**Males (mean value ± SEM)**	**Females (mean value ± SEM)**	***P* value**
Memory				
Mean number of activated pixels		122.69 ± 10.4	71.71 ± 13.2	0.003[a]
	RSPG	46.30 ± 15.3	0.00 ± 0.0	0.007[a]
	RIOG	285.20 ± 47.0	84.20 ± 37.4	0.050[a]
Mean BOLD magnitude		1.35 ± 0.03	1.18 ± 0.06	0.012[a]
	LIPG	1.63 ± 0.13	1.22 ± 0.09	0.016[a]
Spatial attention				
Mean number of activated pixels		237.33 ± 25.3	264.94 ± 57.3	0.660
Mean BOLD magnitude		1.55 ± 0.05	1.56 ± 0.08	0.924
Word generation				
Mean number of activated pixels		328.75 ± 34.2	206.08 ± 27.2	0.005[a]
Mean BOLD magnitude		1.70 ± 0.05	1.37 ± 0.05	0.000[a]
	RDLPFC	1.64 ± 0.14	1.18 ± 0.07	0.028[a]
	LDLPFC	2.05 ± 0.17	1.52 ± 0.19	0.058[b]
	RIPG	1.46 ± 0.21	1.00 ± 0.06	0.046[a]

	CING	1.76 ± 0.18	1.36 ± 0.09	0.056[b]
Motor (left)				
Mean number of activated pixels		116.13 ± 21.3	158.82 ± 33.4	0.290
Mean BOLD magnitude		1.79 ± 0.07	1.76 ± 0.12	0.819
Motor (right)				
Mean number of activated pixels		160.75 ± 26.2	99.58 ± 29.9	0.178
	LSTG	239.00 ± 71.5	68.33 ± 28.1	0.036[a]
Mean BOLD magnitude		1.87 ± 0.07	1.63 ± 0.10	0.053[a]
	RIPG	1.32 ± 0.11	0.88 ± 0.13	0.029[a]
	LIFG	1.44 ± 0.13	0.85 ± 0.10	0.013[a]

Right superior parietal gyrus (RSPG), right inferior occipital gyrus (RIOG), left inferior parietal gyrus (LIPG), right dorsolateral prefrontal cortex (RDLPFC), left dorsolateral prefrontal cortex (LDLPFC), right inferior parietal gyrus (RIPG), cingulate (CING), left superior temporal gyrus (LSTG). [a] $p \leq 0.05$. [b] Trend.

7.4 Discussion

The present study demonstrates specific task-dependent effects of gender on both cognitive performance and on brain activation as measured by both BOLD signal extent and change in the number of pixels. Interestingly, however, our initial hypotheses were not upheld. While we found that males and females did indeed differ in brain activation patterns on several cognitive tasks (but not necessarily on those that we had hypothesized), we found that differences in cognitive performance were not reflected in brain activation, and conversely that changes in brain activation were not reflective of differences in cognitive activation. Recently, Unterrainer et al. (2005) have also found that gender and performance can both influence brain activation independently during a planning task (TOL). In their investigation of both gender influence and individual task performance influence upon brain activity, the authors have observed a positive relationship between brain activity in the right dorsolateral prefrontal cortex and *individual performance* level. Additionally, they have observed sex-specific activation on the task in the right hippocampus. We believe we have expanded upon this investigation by examining the effects of gender and gender performance, as a whole, on the BOLD signal in four tasks assessing different cognitive domains.

Working memory

Men exhibited a larger extent and magnitude of regional brain activation than females during performance of a numerical working memory task. There was a significantly greater regional brain activity in men in the right superior frontal and inferior occipital gyrus (number of pixels) and in the left inferior parietal gyrus (BOLD signal), when compared to women. The increases we observed in the right hemisphere support observations by Speck et al. (2000) during a verbal working memory task of an increased right hemisphere dominance in men (or symmetric activation), compared to the left hemisphere dominance they observed in women during the task. However, unlike Speck et al. (2000), we did not observe a significant difference in performance between the two genders on our working memory task. This would tend to indicate that in men, regardless of performance, there is an increase in regional brain activity during a working memory task, in which the spatial extent of activation is increased in frontal and occipital regions of the right hemisphere.

Spatial attention task

Repeated studies have suggested that males perform better than females on tests of visuospatial functioning (Kimura, 1996). Our results support this, and males in the current study performed with significantly faster reaction times than females. However, the difference in performance between these groups was not accompanied by significant alterations in functional activation. In contrast, although using a radically different and perhaps more challenging visuospatial paradigm, Weiss et al. (2003) observed greater parietal activation in males and greater frontal activation in females challenged with a mental rotation task using fMRI.

Word generation paradigm

Previous studies suggest that males perform better than women in cognitive measures of visuospatial ability, while it is believed that in general females perform better than males in tests of verbal function (Kimura, 1996). In an investigation of verbal fluency using fMRI, Schlosser et al. (1998) observed "no gross differences in activation patterns" between male ($n = 6$) and female ($n = 6$) healthy subjects. However, in the current study, we have observed a significantly increased activation, over the regions involved in carrying out a verbal fluency task, in males compared to females. A regional analysis revealed that a greater BOLD signal magnitude was observed in males, compared to females in several brain regions (right and left dorsolateral prefrontal cortex, cingulate and right inferior parietal cortex). While it would be expected that the female subjects performed better on this verbal task, we do not have performance data due to the nature of the task. In the future, behavioral data would be an asset in the interpretation of this regional brain difference. However, the functional data seem to support that men recruit the prefrontal cortex to a greater degree then women in the performance of this task. Moreover, men have activated the cingulate to a greater degree than females. While we have not assessed differential activity across this structure, in anterior and posterior regions, there are suggestions that parts of the anterior cingulate play an important cognitive role in attending to stimuli and in mediating cognitive interference (Bush et al., 1998). Moreover, Vogt et al. (1992) suggest that the posterior aspects of the cingulate are involved in spatial orientation, memory, and evaluation of sensory stimuli.

Motor tasks

While males and females did not differ in their performance of either the right or left hand finger tapping tasks, there were two regions where males demonstrated a significantly greater BOLD signal magnitude than females during the right hand motor task. This demonstrates an inconsistency between performance measures and functional imaging results, and we are uncertain why these specific regions may be altered during the performance of only one of the motor tasks. However, upon analysis using a two-way ANOVA, we did not actually find that either gender or hand of task had a main effect upon the number of pixels activated or the BOLD magnitude, and this is likely a more significant finding than the separate analyses.

Other male vs. female differences

Several groups have suggested that there are significant differences between males and females functionally in aspects of brain metabolism and cerebral blood flow. Gur et al. (1995) demonstrated a higher cerebral glucose metabolism in males in the cerebellum, basal ganglia, and brainstem and a lower metabolism in the middle and posterior cingulate gyrus. Most studies investigating resting state CBF have largely supported a bias of increased global cerebral blood flow in females (Ragland et al., 2000, Gur and Gur, 1990 and Rodriguez et al., 1988). Regionally, it has been noted that males have a more strongly lateralized cerebral blood flow in frontal regions, in the right hemisphere (Rodriguez et al., 1988), while females have a higher regional cerebral blood flow than males in mid-temporal regions (Ragland et al., 2000).

The reasons that functional differences may exist between men and women are numerous. Several researchers have reported structural differences in limbic areas such as the amygdala and the caudate in male and female children (Durston et al., 2001) as well as in regions of the cingulate, hippocampus, parietal, and occipital regions in adult men and women (Raz et al., 2004). Moreover, it has been reported that women possess a greater proportion of brain grey matter, in comparison to men; although researchers explain that brain volume rather than sex is the main variable in the determination of grey matter volume (Luders et al., 2002). Gur et al. (1999) have also reported a disconnect in the percentages of grey and white matter between men and women. While they report a larger percentage of grey matter in women, they also observed a higher percentage of white matter and cerebrospinal fluid in men. Additionally, they noted that in men and women the correlation between intracranial volume and grey and white matter varied (Gur et al., 1999). The authors suggest that alterations in neural tissue volumes between the sexes may contribute to gender differences in cognitive abilities (Gur et al., 1999).

In addition, there is some evidence to support an endocrine effect upon functional brain activity and brain perfusion (Smith and Zubieta, 2001). In women assessed after treatment with estrogen replacement therapy, Okhura et al. (1995) observed an increase in global cerebral and cerebellar blood flow, compared to a control group of women and modulation of cerebral blood flow during performance of the Wisconsin Card Sorting task has also been observed in women with experimentally manipulated estrogen or progesterone levels (Berman et al., 1997). Dietrich et al. (2001) investigated word stem completion in women (at different times in their menstrual cycle) using fMRI. Their results suggest altered regional brain activation during this task, in women, during the high estrogen phase compared to during menses. Similarly, Shaywitz et al. (1999) observed an altered pattern of functional activation during fMRI of a working memory task in women on estrogen who took part in a double-blind, crossover study and were treated with 21 days of estrogen crossed over with placebo. Unfortunately, because we have not assessed menstrual cycle in the group of females taking part in the current study, we cannot rule out various effects that hormonal influences may have exerted on our results.

Finally, we must consider that physiological differences involved in the generation of the BOLD signal contrast exist between females and males. Indeed, aforementioned structural brain differences and brain composition differences may influence the BOLD signal, as well as regional CBF, blood volume, and cerebral metabolic rate of oxygen (Kastrup et al., 1999). Moreover, recent studies investigating simple visual stimulation in males and females have suggested that a greater number of undetectable BOLD signals are present in *males* than in females (Marcar et al., 2004 and Hedera et al., 1998). However, Marcar et al. (2004) also conclude that while females have a higher CGM than males, this fact is not reflected in the peak of the BOLD signal amplitude. In a similar investigation, Levin et al. (1998) found a decreased BOLD signal response in *females* during binocular visual stimulation, compared to males. They conclude that this is most likely based on a variety of factors influencing blood flow, volume, and oxygenation and also possibly by the fact that lower levels of hemoglobin are observed in females than in males.

The functional imaging literature to date suggests that there are significantly different patterns of activation between men and women on various cognitive tasks and in various paradigms. The current study reinforces the fact that gender matching is essential in functional imaging studies, both clinically and in healthy individuals. Furthermore, it appears that unique patterns of activation between men and women exist during cognitive task performance, which may or may not influence their performance on the task. It is evident that gender-specific changes in functional activation are very much a product of the task performed. However, we must acknowledge that while we believe that this point is well demonstrated by the finding of the current study, we have used a limited sample size for this analysis, and had in particular fewer females take part. The findings, therefore, should be substantiated by further exploration of gender and performance effects on a variety of different tasks using a larger population of female subjects. The fact that we tested fewer females than males in the study may partly explain why regionally there was no accord between gender differences in BOLD signal magnitude changes and the number of activated pixels. Potentially, a larger sample of females would contribute to our ability to distinguish between the genders in a regional analysis.

Taking all of these studies together, along with the findings from the present study, there appears considerable evidence of differences between males and females in brain activation in response to cognitive challenges. They would suggest that in clinical studies of brain activation the sexes should be analyzed separately and that studies should have control populations closely matched for sex distribution. In neuropsychiatric studies, however, interpreting the results can be challenging. While various limbic, subcortical, and cortical dysregulations have been observed in studies of depression, bipolar disorder, and anxiety disorders (for reviews see Silverstone et al., 2005, Haldane and Frangou, 2004, Kanner, 2004 and Anand and Shekhar, 2003), these populations are often biased in terms of gender prevalence (Arnold, 2003, Gavranidou and Rosner, 2003, Cassano and Fava, 2002, Kessler et al., 2001, Piccinelli and Wilkinson, 2000, Brady and Randall, 1999, Pigot, 1999, Weinstock, 1999 and Gold, 1998). As well, because women may seek treatment more than men, it may be easier for a researcher to recruit females. Both of these factors may lead to a patient sample predisposed to an uneven gender distribution.

In conclusion, the functional imaging literature to date suggests that there are significantly different patterns of activation between males and females on various cognitive tasks and in various paradigms. The current study reinforces the fact that gender matching is essential in clinical functional imaging studies, and supports the idea of exploring male and female populations as distinct groups.

(A version of this chapter has been published – see Bell et al.,(2006), Neuroimage, 30: 529-538)

We have shown in that males and females differ on brain activity measures across a variety of cognitive tasks. However, we have also shown that the both gender and performance of tasks may impact functional imaging results; however this occurs in an inconsistent manner across different tasks. It is difficult to predict the impact of either gender or performance, or their interaction, on brain activation across a study, but both of these factors should be considered when assessing functional imaging data.

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SECTION III

Chapter 8. Hemispheric functional asymmetry in major depression tested by executive function tasks.

8.1 Introduction

A wide range of studies to date support the occurrence of state- and trait- related cognitive deficits in patients suffering from MDD. Moreover, deficits along some cognitive domains are associated with increased recurrence and more chronic course of disease (Gualtieri et al., 2006; Fossati et al., 2002;). Consistently, neuropsychological testing in patients has demonstrated deficits in explicit memory, attention and psychomotor speed (Gualtieri et al., 2006; Paelecke-Habermann et al., 2005; Ottowitz et al., 2002). In addition, the majority of studies find that MDD patients have impaired performance on tests of executive function (Austin et al., 2001).

To test executive function is essentially to test problem-solving skills (Fossati et al., 2001). In this domain, tasks of executive function require planning, monitoring and execution of goals (Elliott, 2003). Depressed patients express a deficit in executive function which is exposed by their poor performance compared to healthy individuals on tests such as the WCST, the TOL test, the Stroop test and the Intrademensional/extradimentional (ID/ED) set shift task (for a full review see Ottowitz et al., 2002).

It has been suggested that executive function tasks evaluate frontal lobe function, because damage of the prefrontal cortex, in particular, results in deficits to planning, decision-making, and organization (Elliott, 2003; Funahashi, 2001) as well as impaired performance on tests of executive function (Elliott, 2003). Moreover, in HCs, neuroimaging studies of executive function have repeatedly shown activation of the prefrontal cortex, specifically the DLPFC (Ottowitz et al., 2002). However, researchers also propose that executive functions are controlled by intimate circuits between the prefrontal cortex and striatum, cautioning against the implication that executive function tests are simply "frontal lobe tests" (Elliott, 2003).

Functional imaging of the resting brain in depression has revealed many abnormalities of cerebral metabolism and cerebral blood flow, including hypoactivity in the dorsal prefrontal cortex and anterior cingulate cortex (ACC) and hyperfrontality of the ventral prefrontal cortex (Drevets, 2000; Rubin et al., 1995; Mayberg 1997; Mayberg et al., 1994; Biver et al., 1994; Bench et al., 1993; Dolan et al., 1992; Baxter 1989). In line with these observations, Mayberg and colleagues have suggested that dysregulation of dorsal structures mediates the cognitive deficits of attention and executive function in depression while the ventral components mediate the vegetative symptoms of the disorder (Mayberg et al. 2003). There is, however, a less comprehensible literature of brain activation alterations in MDD patients while engaging in cognitive tasks of executive function (Rogers et al., 2004). Collectively, these studies have examined patients on the WCST, the TOL, Stroop and ED/ID tasks and on tests of verbal fluency (Rogers et al., 2004). Few studies have demonstrated positive findings indicative of a functional difference between patients and healthy controls. Differences that have been observed are contradictory and include hypoactivity of Broadmann's areas 6, 9, 10, 46 (dorsal aspects of frontal lobe), hypoactivity of the ACC (Goethals et al., 2005; Okada et al., 2003; Audenaert et al., 2002; Elliott et al., 1997) and hyperactivity of both ACC and left DLPFC (Wagner et al., 2006).

The current study was designed to assess dysregulations in function of the prefrontal cortex in MDD during a range of executive function tasks. We hypothesized, based on models of dysfunction in MDD in the literature, that a comparison to healthy volunteers would demonstrate hypoactivity of the DLPFC and hyperactivity of the VLPFC and medial prefrontal cortex (mPFC) in MDD.

8.2 Methods

This study was approved by the Health Ethics Board at the University of Alberta, Faculty of Medicine and Dentistry and all subjects gave full informed consent.

8.2.1 Subjects

Sixteen patients suffering from MDD (aged 18-65) were recruited from a mood disorders rapid referral program run by Dr. Peter Silverstone between February 2006 and March 2007. A full personal and family history was obtained and diagnosis was made using Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) criteria for BP (American Psychiatric Association, 1994), using the structured clinical interview for DSM-IV (SCID). Symptom severity for depression was determined using the 17-item Hamilton Depression rating scale (HAM-D) (Hamilton, 1960), and the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Absence of manic symptoms was confirmed by the Young Mania Rating Scale

(YMRS) (Young *et al.*, 1978). Past and present drug use was assessed and subjects were excluded based on current abuse of these substances.

Fifteen HCs were recruited from the graduate and undergraduate population through university advertisements. Subjects gave a medical history, and underwent screening by the structured clinical interview for DSM-IV (American Psychiatric Association, 1994) to rule out past or present psychiatric illness. Past and present drug and alcohol use was assessed and subjects were excluded based on current abuse of these substances.

8.2.2 Study Design and Tasks

Patients and HCs underwent one functional magnetic resonance imaging (fMRI) scan, and brain activation was measured as they performed three different tasks.

Tasks:

The three tasks; WCST, the TOL test, and a verbal fluency task based on a modification of the Controlled Oral Word Association FAS Test (COWAT-FAS) were administered in a blocked design. Each was presented to the subjects visually by projection (Epson ELP-7000) onto a screen viewed while in the magnet. E-prime software was used to create and present paradigms, as well as to collect behavioural responses made by keypad (Cedrus RB-620). The WCST consisted of nine blocks (4 active tasks (110 sec each) and 5 control task (50 sec each)), the TOL task consisted of eight blocks (4 active tasks (60 sec each) and 4 control blocks (40 sec each)) and the verbal fluency task consisted of eleven blocks (5 active tasks (50 sec each) and 6 control task (50 sec each)).

Wisconsin Card Sorting Task (WCST):

The functional paradigm for testing WCST was based on a previous paradigm employed by Riehemann et al. (2001). In the active block, subjects were required to match a target card to one of four fixed cards. Each of the cards depicted a specific combination of form, color, and number. Instructions were given to match each new target card to one of the four fixed cards, but subjects were not told by which dimensions the cards should be matched. Predetermined criteria existed and the experiment required that they match first based on the color of the forms. Subjects received feedback once a card was matched and would be required to modulate their next response based on the "correct" or "incorrect" feedback provided. Through trial and error if subjects correctly solved the criteria of matching, and matched **6 cards** correctly in a row, then the criteria would change to form and once 6 problems were again solved then the criteria would change to number. This would be repeated through each block, and the speed and number of problems solved was determined by the subjects' responses in the time allotted. In the control block, subjects were again required to match a target card to one of four fixed cards. In the control task, however, the cards only varied on one dimension (color) and there was only one criteria by which subjects could match (match the color of the target card to one of the four fixed cards). See *Figure 8.1* for an illustration of the active and control tasks.

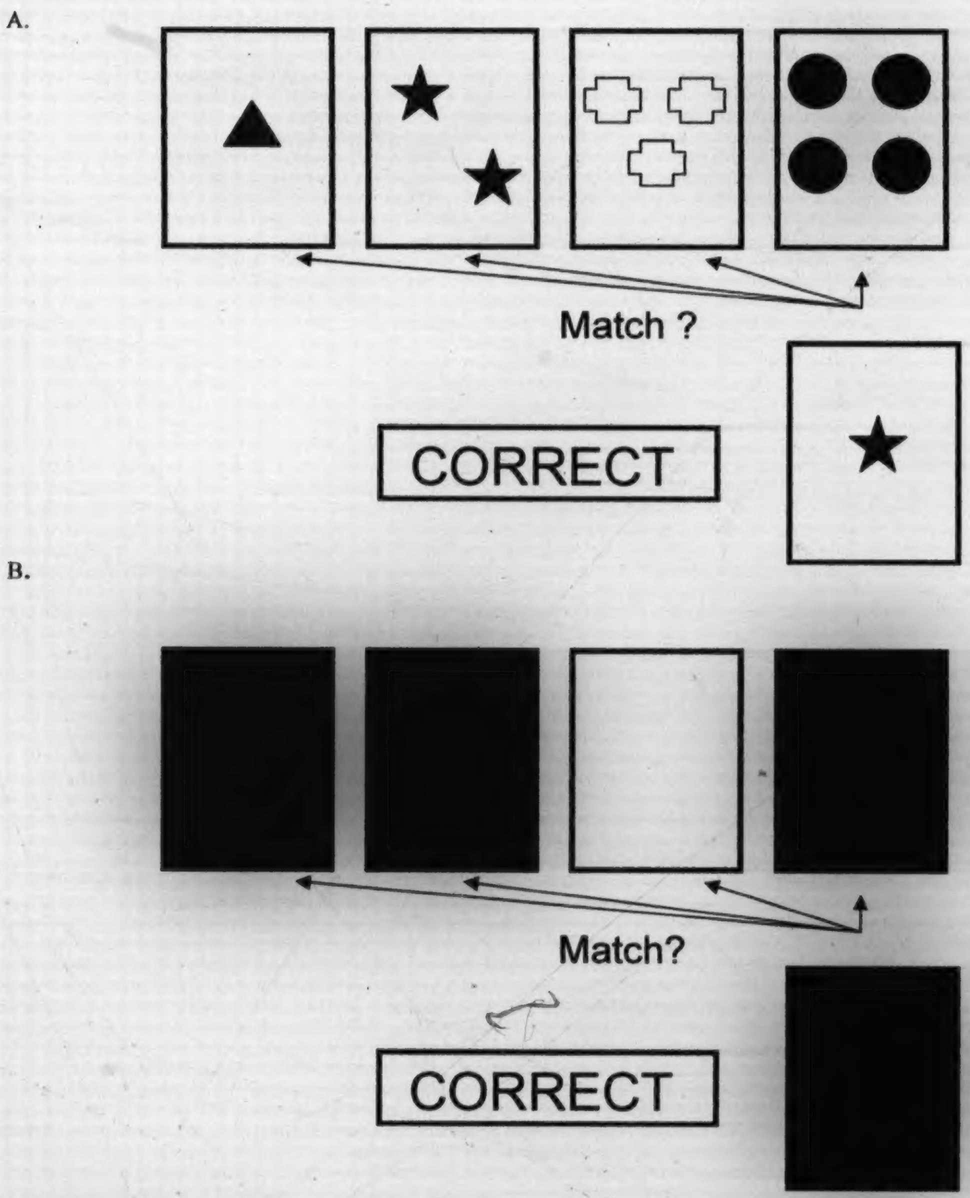


Figure 8.1A : The Wisconsin Card Sorting Task (WCST): active condition. B. Wisconsin Card Sorting Task (WCST) control condition. *Subjects must choose one of the static top four cards to match with the dealt bottom card. They modulate their response based on correct or incorrect feedback provided after each matching choice.*

The Tower of London Task (TOL)

The TOL task was based on a previously developed paradigm published by Van den Heuvel et al. (2003). The active block required that subjects calculate (in their heads) the minimum number of moves of a set of balls (one red, one blue, one green) required to get from a start configuration where the balls are distributed among three unequal length pegs to a goal configuration where the balls are distributed in a different way on the three pegs. Subjects are required to follow two rules; first, a ball cannot be moved from underneath others and second, that the longest peg can hold three balls but that the second and third pegs can only hold two and one balls respectively at any given time. Upon calculating their answer, subjects are required to choose this answer from two given numbers on the screen. The control block was visually similar in that there were two configurations containing different distributions of balls (many red, blue and green) on pegs. In this task subjects were instructed to count the number of blue and red balls across both configurations and choose the corresponding answer from two numbers given. See *Figure 8.2* for an illustration of the active and control components of the task.

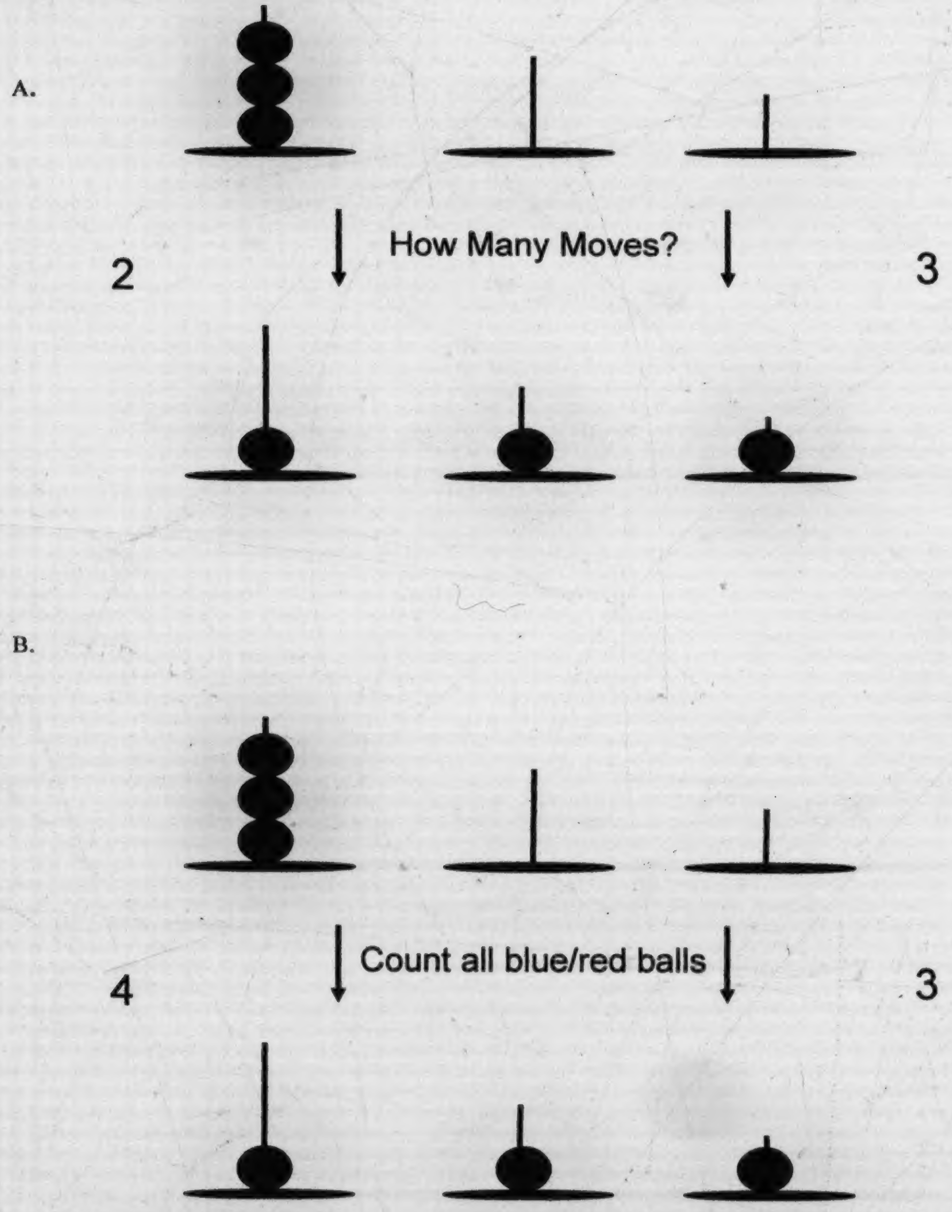

A.
2
How Many Moves?
3
B.
4
Count all blue/red balls
3

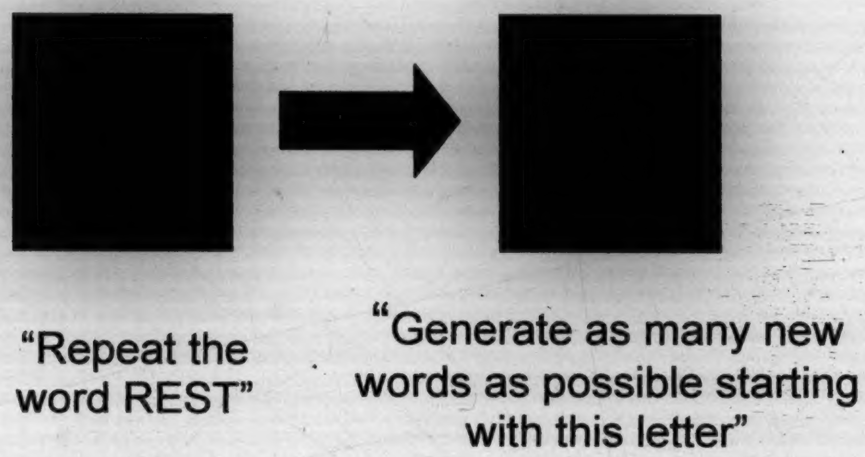
***Figure 8.2A : The Tower of London (TOL) active condition**. Subjects determine the minimum number of moves to get balls from top configuration to bottom and choose from 2 answers on either side of the screen.* ***B. The Tower of London (TOL) control condition**. Subjects count the number of red and blue balls on the screen and choose answer from 2 answers on either side of screen.*

The Verbal Fluency task:

The verbal fluency task was modulated from a previous word generation task our research team has used (Bell et al. 2005, Willson et al., 2004) and intended to replicate more closely the FAS component of the COWAT. In the active block a series of letters (biased towards presenting the letters F, A and S) were randomly chosen from the alphabet and presented at 4-second intervals. Subjects were instructed to generate as many words as possible beginning with each letter during the time allotted. In the control block subjects viewed the word "REST" on the screen and were asked to repeat the word 'REST' silently, slowly and consistently until the end of the block. See *Figure 8.3.*

Figure 8.3: Verbal fluency control and active tasks.

In the control condition subjects repeat the word "rest" until the word is removed from the screen and replaced by the active condition where subjects generate as many words as possible starting with the given letter.


"Repeat the word REST"
"Generate as many new words as possible starting with this letter"

8.2.3 Behavioral Measurements

Behavioural measurements were collected using E-prime software (version 1).

Reaction Time (RT):

The average RT to response was collected for the active and control conditions in the WCST and TOL tasks. In the verbal fluency task, the average number of words generated (active) and average number of times the word REST was repeated (control) were collected.

Errors:

The number of errors was collected for the active and control conditions of the TOL task. In the active portion of the WCST, non-perseverative and perserevative errors were collected separately. Additionally, the number of errors in the control portion of the task was collected.

Number of problems solved:

In the WCST and TOL tasks, the numbers of problems solved in each of the control and active blocks were collected.

All behavioural measures were compared between patients and healthy controls using independent samples t-tests ($p \leq 0.05$).

8.2.4 Image Acquisition

The fMRI study was conducted on a 1.5-T Siemens Sonata scanner (Siemens, Erlangen, Germany) with a single shot eco-planar image (EPI) gradient echo sequence (TR = 2500ms, TE = 50msec, 3.4 x 3.4 x 4.0mm) to acquire 26 contiguous slices obtained at an oblique angle along the AC-PC line. A high resolution T1-weighted magnetization prepared rapid gradient echo sequence was also acquired during the imaging session to overlay the functional analysis.

8.2.5 fMRI Data Analysis

fMRI data analysis was conducted according to previously published methods (Willson et al., 2004, Bell et al., 2005). Pre-processing and analysis was performed using Statistical Parametric Mapping (SPM), 1999 version (SPM99 - Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during pre-processing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 x 8 x 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2* weighted realigned EPI functional images. Functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between subject variability and allow Gaussian random field theory to give corrected statistical inferences (Friston et al 1994). Initially a design matrix was created for each task and applied individually to each subject for analysis. A corrected threshold (p = 0.05) was applied to the analysis of the Verbal Fluency task, and an uncorrected threshold (p = 0.001) was applied to the more conservative activation maps observed in the WCST and the TOL task. Additionally, within each design matrix the data were high pass filtered to remove low-frequency drifts in the signal and low pass filtered using the hemodynamic response function to remove high frequency noise. The data were proportionally scaled to a global mean of 100.

For each subject the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels and BOLD signal magnitude within each region of interest (ROI). Image ROIs were constructed using automated anatomical labeling (AAL) software (Tzourio-Mazoyer et al., 2002), running with MRIcro (Rorden and Brett, 2000). ROI boundaries were determined from previous literature resulting in five areas of interest; the right and left DLPFC (BA 9 and 46), the right and left VLPFC (BA 44,45 and 47), and the mPFC (BA 24, 25 and 32) (Goethals et al., 2004). Each ROI was then smoothed in SPM99 with an equivalent kernel (8mm) as the functional EPI images.

Within each ROI, in each task, the number of activated pixels was determined using a SVC. The BOLD signal magnitude in each ROI was determined using the MARSBAR toolbox for SPM (Brett et al 2002). The magnitude of the signal was calculated across a seven-voxel sphere centered on the *most* significantly active voxel in each ROI. The fitted response (or BOLD signal intensity change) is expressed in percentage of whole brain mean. Because the global brain mean in the voxel-wise analysis was scaled to 100, this signal change represents the percentage of signal change with respect to the global mean intensity of the scaled images. Subsequently statistical calculations for BOLD signal magnitude were based on the average response calculated from the plateau portion

7

of the hemodynamic response (eight seconds after stimulus origination until stimulus termination) (Willson et al., 2004).

Comparisons of the number of activated pixels and BOLD signal were carried out using independent samples t-test between MDD patients and healthy controls. This comparison was made for the medial prefrontal cortex (mPFC) directly. Comparisons between the four regions of interest in the lateral prefrontal cortex (lPFC) were made by calculating the relative ratio of activity in one ROI vs the other areas. Student's t-tests were then used to compare these ratios between MDD patients and healthy volunteers and significance was set at $p \leq 0.05$.

8.3 Results

8.3.1 Subjects

Sixteen patients (10 females, 6 males) and fifteen healthy controls (7 females, 8 males) underwent a functional imaging scan. The patients were on average older (mean ± S.D.; 37.6 ± 10.1) than the healthy subjects (26.0 ± 3.6). However, the difference did not exceed one standard deviation. Patients had a Hamilton depression rating score (mean ± S.D.) of 19.7 ± 4.4, compared to healthy volunteers whose scores were negligible (0.8 ± 1.1). MDD patients were significantly more depressed ($p< 0.01$) with a MADRS score of (mean ± S.D.) 26.1 ± 5.4 than healthy controls (0.2 ± 0.1). In manic symptoms, assessed by theYMRS, our patients scored (mean ± S.D.) 1.88 ± 2.0 and healthy controls scored 0.07 ± 0.3. Data from one healthy subject had to be discarded on the task of verbal fluency, and data from one patient also appeared corrupt on the WCST. Two patients were unable to complete the TOL task due to the complex nature of the problems and therefore their data were excluded. Patients were on a variety of medications: fifteen were taking antidepressants, and five were receiving concomitant treatment with antipsychotics.

8.3.2 Functional Imaging Results

Wisconsin Card Sorting Task (WCST):

There were no significant differences between patients and healthy subjects on measures of either the number of activated pixels or the BOLD signal magnitude in the mPFC. Additionally, comparisons of the ratio of activation in the right and left lPFC revealed no significant differences between MDD patients and volunteers.

Verbal Fluency Task:

There were no significant differences between patients and healthy subjects on measures of the number of activated pixels or the BOLD signal magnitude in the mPFC. Comparisons between the right and left lPFC revealed significant differences between MDD patients and healthy controls in the right DLPFC and the left VLPFC. MDD patients demonstrated significantly greater relative activation of the right DLPFC ($p = 0.01$) by the number of activated pixels (mean ± S.E.; 0.21 ± 0.03; see Figure 8.4) and demonstrated a trend to significantly increased relative activity ($p = 0.08$) in the right DLPFC by the BOLD signal magnitude (0.32 ± 0.04, see Figure 8.5), compared to healthy controls (0.11 ± 0.02, 0.23 ± 0.03 ; respectively). MDD patients also demonstrated significantly reduced relative activity ($p = 0.04$) in the left VLPFC by the

BOLD signal magnitude (mean ± S.E.; 0.35 ± 0.05; see Figure 8.7) and a trend to significant decrease in relative activity (p = 0.06) in the left VLPFC by the number of activated pixels (0.56 ± 0.09; see Figure 8.6), compared to healthy controls (0.47 ± 0.03, 0.89 ± 0.14; respectively).

Figure 8.4: The relative ratio of activity (number of activated pixels) in the right DLPFC (RDLPFC) in MDD patients and healthy controls in the verbal fluency task.

** equals p-value significant ≤ 0.05 level between group comparison of MDD patients and controls.*

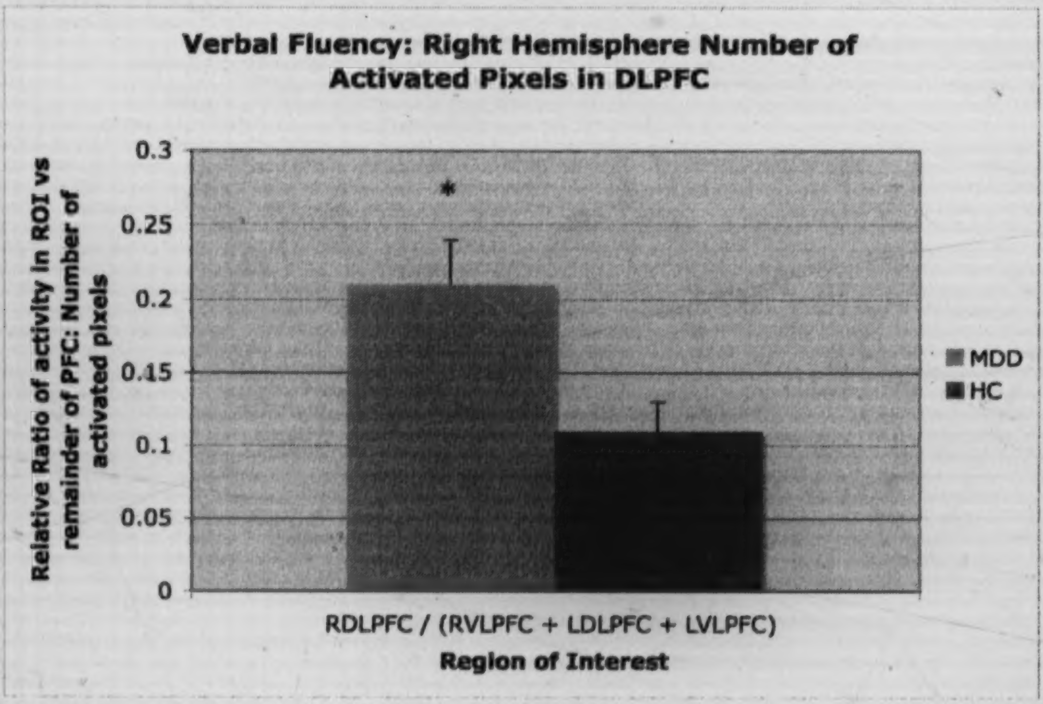


Figure 8.5: The relative ratio of activity (percent BOLD signal) in the right DLPFC (RDLPFC) in MDD patients and healthy controls in the verbal fluency task.

*** equals p-value trend to significance p ≤ 0.09 between group comparison of MDD patients and controls.*

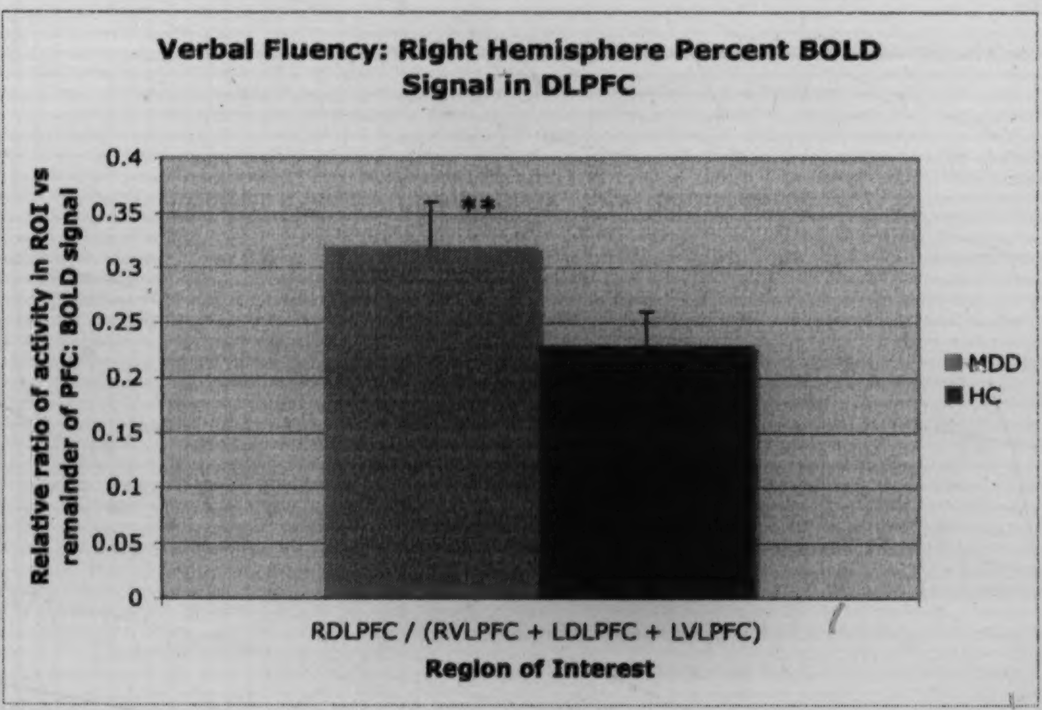


Figure 8.6: The relative ratio of activity (number of activated pixels) in the left VLPFC (LVLPFC) in MDD patients and healthy controls in the verbal fluency task.

*** equals p-value trend to significance p ≤ 0.06 between group comparison of MDD patients and controls.*

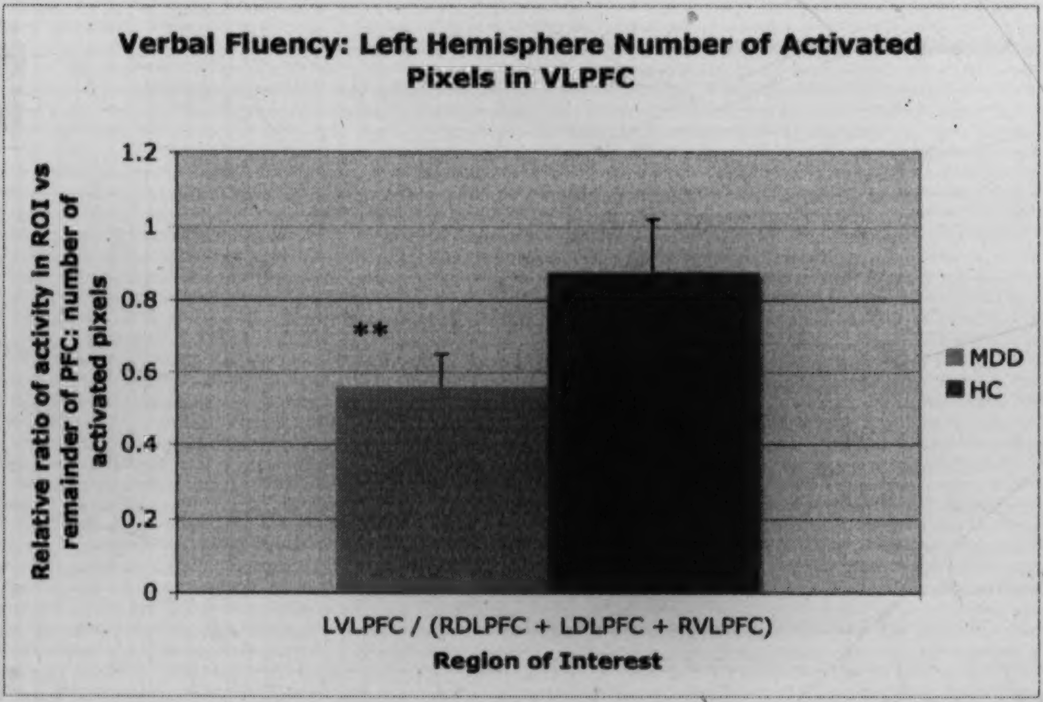
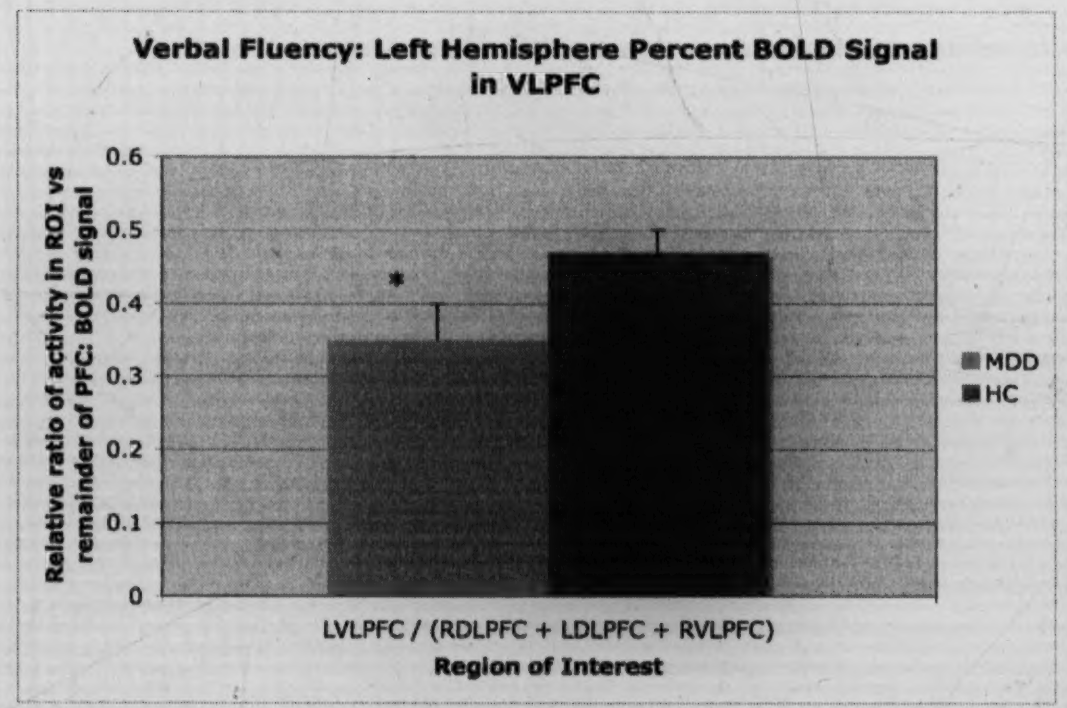


***Figure 8.7:* The relative ratio of activity (percent BOLD signal) in the left VLPFC (LVLPFC) in MDD patients and healthy controls in the verbal fluency task.**

** equals p-value significant $p \leq 0.05$ level between group comparison of MDD patients and controls.*



Tower of London (TOL) Task:

There were no significant differences between patients and healthy subjects on measures of the number of activated pixels or the BOLD signal magnitude in the mPFC. Comparisons between the right and left lPFC revealed significant trends between MDD patients and healthy controls in the right VLPFC and the left DLPFC. There was a trend to significant relative increase in MDD patients in the right VLPFC (p = 0.08) by the number of activated pixels (mean ± S.E.; 0.38 ± 0.04; see Figure 8.8 and Figure 8.9) compared to healthy controls (0.26 ± 0.05). Additionally, there was a trend to significant relative decrease in MDD patients in the left DLPFC (p = 0.09) by the magnitude of the BOLD signal (mean ± S.E.; 0.33 ± 0.02, see Figure 8.10 and 8.11), compared to healthy controls (0.51 ± 0.1).

Figure 8.8: The relative ratio of activity (number of activated pixels) in the right VLPFC (RVLPFC) in MDD patients and healthy controls in the TOL task.

*** equals p-value trend to significance $p < 0.08$ between group comparison of MDD patients and controls.*

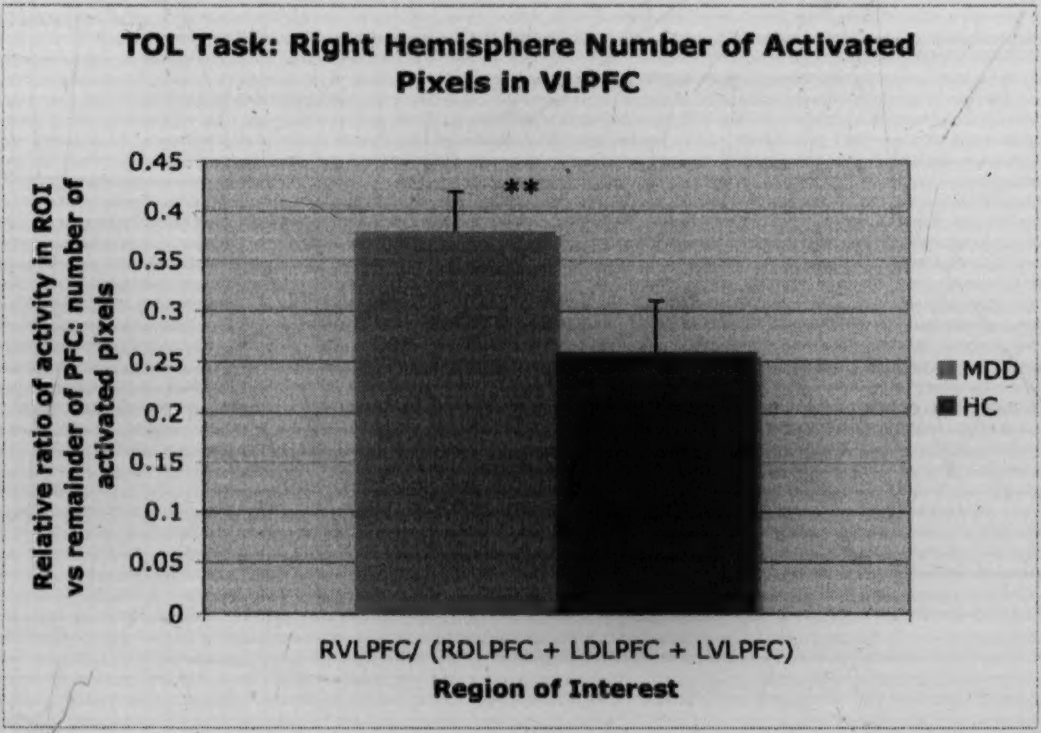


Figure 8.9: The relative ratio of activity (percent BOLD signal) in the right VLPFC (RVLPFC) in MDD patients and healthy controls in the TOL task.

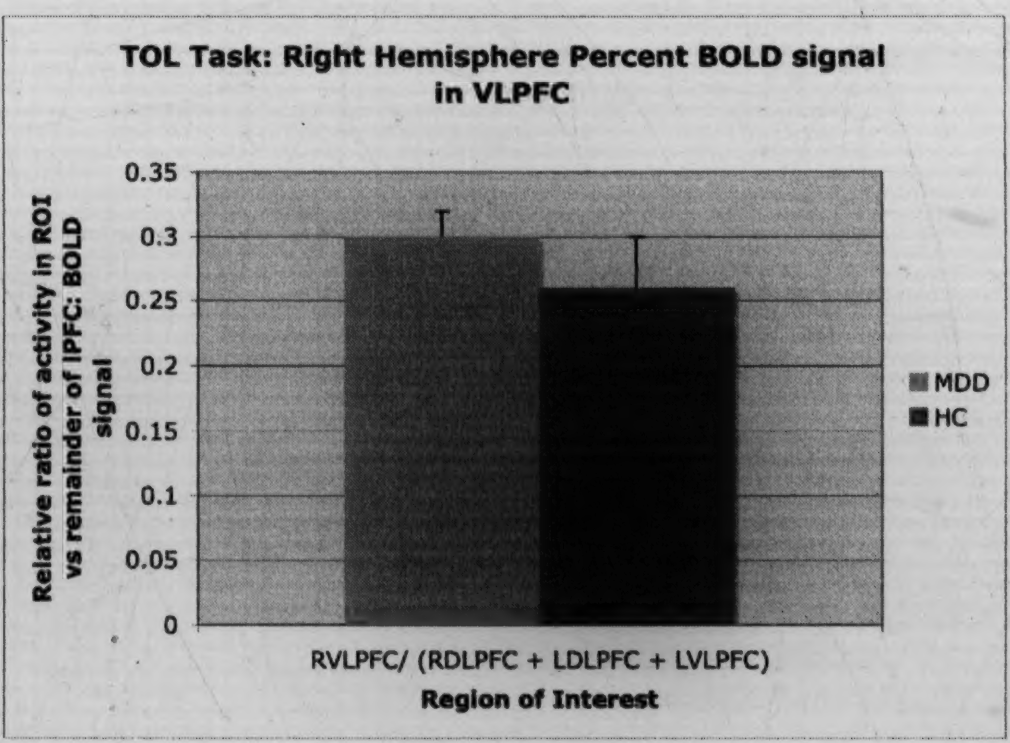


Figure 8.10: The relative ratio of activity (number of activated pixels) in the left DLPFC (LDLPFC) in MDD patients and healthy controls in the TOL task.

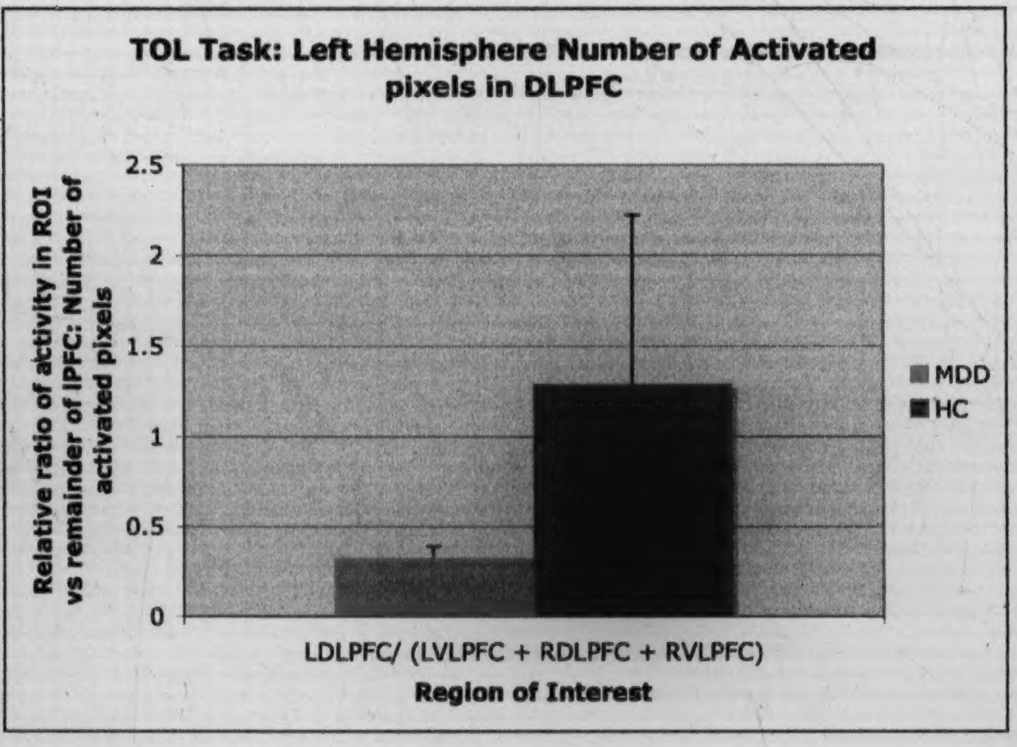
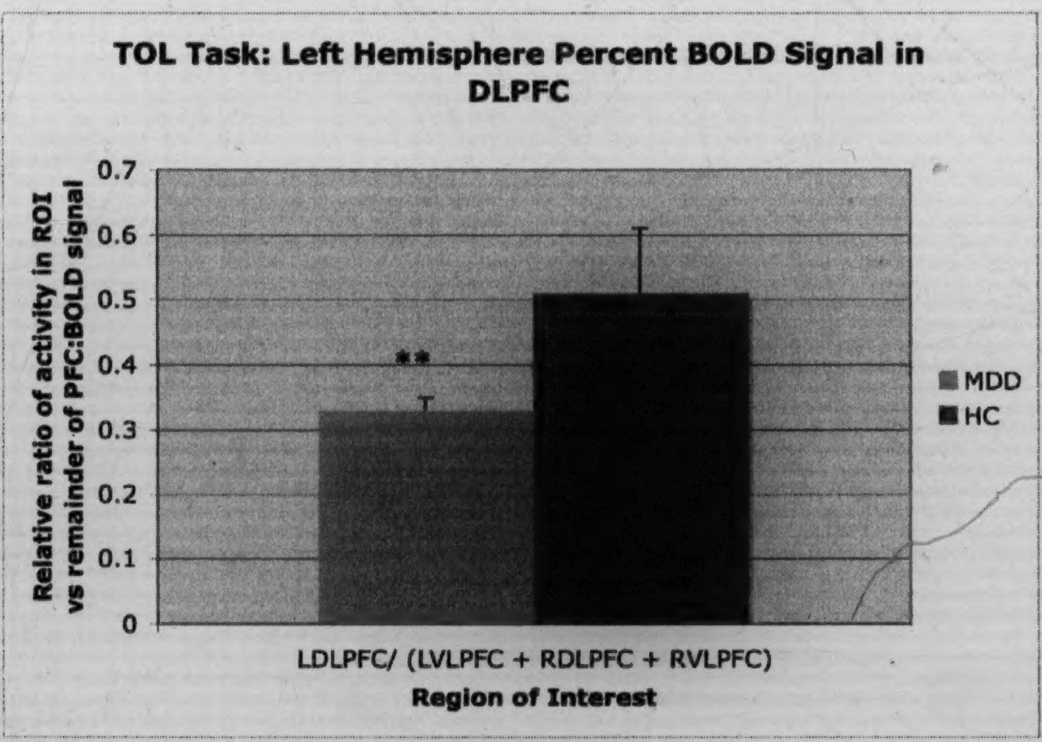


Figure 8.11: The relative ratio of activity (percent BOLD signal) in the left DLPFC (LDLPFC) in MDD patients and healthy controls in the TOL task.

*** equals p-value trend to significance p < 0.09 between group comparison of MDD patients and controls.*



8.3.3 Behavioral Measurements

Reaction Time (RT):

Patients were significantly slower performing the active and control conditions of the WCST ($p < 0.01$, $p < 0.01$). There were no significant differences between patients and volunteers for average RT on the TOL task either control or active condition. Patients did generate on average fewer words than healthy volunteers during the verbal fluency task blocks ($p = 0.03$). See Table 8.1, 8.2 and 8.3.

Errors:

There was no difference in the number of perseverative or total errors in the WCST, or in the control task, in patients compared to healthy controls. Patients and volunteers did not significantly differ on the number of errors in either the active or control portions of the TOL task. See Table 8.1, 8.2 and 8.3.

Number of problems solved:

In the WCST, patients solved fewer problems overall than healthy controls in the active ($p < 0.01$) and control ($p < 0.01$) conditions. There were not significant differences between patients and healthy controls in the number of problems solved in the TOL task, active or control conditions. See Table 8.1, 8.2 and 8.3.

Table 8.1: Behavioral data, performance on WCST active and control tasks. *Values represent mean ± S.E. * represents significant difference between MDD patients and healthy controls.*

		Healthy Controls (n = 15)	Major Depression Patients (n= 16)
Number of cards/problems solved	Control WCST	111.2 ± 1.5	100.0 ± 2.0 *
	Active WCST	100.1 ± 2.1	92.0 ± 2.0 *
Average RT (msec)	Control WCST	767.4 ± 31.0	1011.4 ± 48.3 *
	Active WCST	1478.5 ± 94.8	1889.8 ± 107.2 *
Number of Errors	Control WCST	1.8 ± 0.5	3.1 ± 0.7
	Active WCST	7.3 ± 1.6 (perseverative) 29.5 ± 2.3 (total)	11.0 ± 1.3 (perseverative) 34.2 ± 2.2 (total)

Table 8.2: Behavioral data, performance on verbal fluency active and control tasks.

*Values represent mean ± S.E. * represents significant difference between MDD patients and healthy controls.*

		Healthy Controls (n = 15)	Major Depression Patients (n= 14)
Number of generated words /repeats	Control Verbal Fluency	107.8 ± 9.7	116.3 ± 17.1
	Active Verbal Fluency	73.1 ± 5.5	59.1 ± 4.6
Average number of repeats/words per block.	Control Verbal Fluency	6.8 ± 0.5	6.6 ± 1.0
	Active Verbal Fluency	5.1 ± 0.3	4.2 ± 0.2 *

Table 8.3: Behavioral data, performance on verbal fluency active and control tasks.

*Values represent mean ± S.E. * represents significant difference between MDD patients and healthy controls.*

		Healthy Controls (n = 15)	**Major Depression Patients (n= 14)**
Number of problems solved	Control TOL	48.9 ± 2.8	47.1 ± 2.8
	Active TOL	20.8 ± 1.4	19.6 ± 1.4
Average RT (msec)	Control TOL	3315.7 ± 200.4	3405.7 ± 194.5
	Active TOL	10267.4 ± 475.9	10969.3 ± 742.0
Number of Errors	Control TOL	2.4 ± 0.7	1.2 ± 0.4
	Active TOL	4.6 ± 0.5	6.64 ± 1.9

8.4 Discussion

The present study has demonstrated that MDD patients functionally recruit the right prefrontal cortex more and the left prefrontal cortex less than HCs during the completion of executive function tasks.

Before this study, there were only limited data examining the functional changes occurring in depressed patients during the performance of executive function tests. Using a TOL paradigm administered to a small sample of depressed patients, Elliott and colleagues (1997) observed a decreased activation in left and right DLPFC, compared to healthy individuals, assessed by PET scanning. In 2005, this finding was supported by a SPECT study (Goethals and al., 2005) showing decreased activity in dorsolateral prefrontal regions in depressed patients engaging in a TOL task. However, using a different executive paradigm, the Stroop task, researchers have also found that the left DLPFC is recruited in depressed patients, but not in HCs, carrying out the task (Wagner et al., 2006).

Particularly relevant to the findings of our study are two previous fMRI studies, which suggest that hemispheric asymmetries exist in depressed patients engaged in executive function. The first, a study of verbal fluency, found that depressed patients activated the left DLPFC less than a group of HCs (Okada et al., 2003) and the second, a recent study of adolescents (8-15 years old) completing the Stroop task, found a significant correlation between severity of depressed mood and increased activity in the left DLPFC, accompanied by a correlation with decreased activity in the right DLPFC

(Killgore et al., 2007). Our findings of a *right* hemisphere dominance during executive function tasks in depressed patients seems to contradict the results of Killgore et al. (2007) demonstrating a *left* hemisphere dominance in depressed patients. However, in discussion of their results Killgore and colleagues (2007) suggest that the finding of increased left hemisphere activity actually reflects a compensatory mechanism during task completion to accommodate for a baseline reduction in activity in this hemisphere.

We believe our current study is more comprehensive when compared to previous studies. In particular, it should be cautioned that each of these previous studies, aside from Killgore et al. (2007), are results from small samples of depressed patients (6-10 patients). Additionally, each study assessed subjects based on functional maps acquired during only one task. The current study, we believe, depicts a more thorough examination of executive function in depression, as it was explored by a battery of tests.

There is a convergence of evidence from lesioned patients, EEG research and functional imaging studies which suggests that hemispheric asymmetries exist within the context of emotional processing in the brain (Rotenberg, 2004). The data in support of hemispheric lateralization in emotion, and theorized by Davidson in the early 1990's, began to accumulate in EEG studies of depressed patients who demonstrated hypoactivity of the left prefrontal cortex or hyperactivity of the right prefrontal cortex (Flor-Henry et al., 2004; Debener et al., 2000; Davidson 1999; Pauli et al., 1999; Gotlib et al., 1998; Drevets 1998; Bell et al. 1998; Bruder 2003; Bruder et al., 1997; Bench et al., 1992; Henriques and Davidson 1991; Bruder et al., 1989; Schaffer et al., 1983). This was accompanied by evidence in healthy volunteers demonstrating a right hemispheric activation bias to negatively valenced paradigms (Wheeler et al. 1993; Davidson et al., 1990; Ahern et al., 1985; Tucker et al., 1981). Parallel evidence of a right hemisphere dominance in negative emotion processing and a left hemisphere dominance in positive emotion processing was collected by observing patients suffering from unilateral cortical lesions (Braun et al., 1999; Gainotti, 1972; Starkstein and Robinson, 1988) . Within this literature, the findings of Braun et al. (1999) in the examination of over one hundred subjects with unilateral lesions supports an association between the occurrence of left hemisphere lesions and clinical depression. More evidence of a cerebral asymmetry in emotion comes from fMRI, in a study by Canli et al. (1998) where healthy volunteers demonstrated increased left frontotemporal activity to positive emotional stimuli and increased right inferior frontal activity to negative stimuli.

While it is well established from EEG and functional neuroimaging studies that depressed patients demonstrate hypoactivity of the left hemisphere at rest (Debener et al., 2000; Davidson 1999; Pauli et al., 1999; Reid et al., 1998; Gotlib et al., 1998; Drevets 1998; Bell et al. 1998; Bruder et al., 1997; Henriques and Davidson 1991; Schaffer et al., 1983), our study lends support to the idea that this hemispheric asymmetry is maintained in depressed patients carrying out executive function tasks such that the right hemisphere is hyperactive and the left hemisphere is hypoactive during cognitive performance. It is possible that this asymmetry underlies some of the deficit that is observed in depressed patients who perform poorly in executive function tasks.

However, there is inconsistency in the behavioural data in our study that poses a challenge to the interpretation of the functional results. Depressed patients only demonstrated a behavioural deficit on some of our tasks of executive function, and their deficits were less than expected. Previous neuropsychological evidence supports the idea that depressed patients perform more poorly than healthy controls on the TOL task and WCST (Merriam et al., 1999, Harvey et al., 2004, Austin et al., 1992, Axelrod et al., 1994, Franke et al., 1993, Beats et al., 1996, Austin et al., 2001, Elliott et al., 1996, Purcell et al., 1997). While we did observe significant deficits along some of the dimensions of problem solving in the WCST, we would have additionally expected to observe an increase in the number of perseverative errors by patients in this task based on the literature (Austin et al., 2001, Merriam et al., 1999, Harvey et al., 2004). In addition we did not observe any deficits in a comparison of patients and healthy controls in the TOL task. However, in reference to the TOL task, we believe that this lack of differences might be due to the difficulty of the task. It was clear from the behavioural evidence that both patients and healthy controls found this task to be challenging and this may have prevented our ability to tease out a significant performance effect on behalf of the patients. There is less evidence of a neuropsychological dysfunction in verbal fluency in depressed patients (Harvey et al., 2004, Austin et al., 2001, Beats et al., 1996, Elliott et al., 1996). We did, however, observe that patients were unable to generate the same average number of words as HCs over the course of the task.

In looking at the functional results along with the behavioural data, we are unable to say that the functional alterations specifically reflect a deficit in performance in patients along these tasks. Rather, it would appear that functional brain activity is altered in depressed patients performing executive function tasks independent of behavioural success or failure on the same tasks. However, it should be acknowledged that paradigms completed in the scanner are never identical to neuropsychological tests examined outside of the scanner; methodologically this is not possible. The fact that patients perform the tasks in a block manner, alternated with a control task, at a set pace over the course of an hour without a break, may potentially affect our ability to pick up the behavioural deficits as they are in cognitive batteries. The goal, therefore, of the behavioural data becomes to assure that patients and volunteers have been engaging in the tasks for which functional activity maps are desired.

The current study demonstrates that depressed patients display a hemispheric bias towards processing information in the right hemisphere compared to healthy subjects. We suggest that the increased brain activity we observed in depressed patients in the right hemisphere during executive function tasks further reflects the occurrence of hemispheric asymmetries in this population.

Our observations in this study are not consistent with our expectation of decreased dorsal prefrontal cortex activation in MDD patients. Instead we have consistently observed a bias towards increased right hemisphere prefrontal activity in MDD patients, which coincides with the right hemisphere model of negative affective processing.

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Chapter 9. Right dorsolateral prefrontal cortex (DLPFC) hyperactivity during executive function tasks in major depression vs bipolar II depression.

9.1 Introduction

Patients with mood disorders often complain of difficulties maintaining attention and report memory deficits (Martinez-Aran et al., 2005; Purcell et al., 1997). However, these reports may not even adequately identify the amount of cognitive dysfunction that patients truly experience (Martinez-Aran et al., 2005). Neuropsychological testing reveals that patients with major depression suffer a wide range of deficits in the domains of memory, attention, psychomotor speed and executive function (Gualtieri et al., 2006; Paelecke-Habermann et al., 2005; Ottowitz et al., 2002) and that these deficits may diminish upon remittance of their symptoms (Borkowska and Rybakowski, 2001). Patients suffering from BP also experience a range of deficits in memory, attention, verbal fluency and executive function (Martinez-Aran et al. 2004; Martinez-Aran et al., 2002). However, unlike the observations made in unipolar depressed patients, evidence suggests that cognitive decline in verbal memory and executive function persists in bipolar patients throughout bipolar states (mania and depression) as well as in the remitted euthymic state (Martinez-Aran et al., 2004). More recently, evidence suggests that memory difficulties may be persistently observed across all phases of the illness (Mahli et al., 2007).

In comparison, during acute episodes of depression, bipolar patients display a significantly greater deficit on measures of executive function; the WCST, the Stroop test, verbal fluency, and TMT, than their unipolar counterparts (Borkowska and Rybakowski, 2001). Earlier studies, however, had been inconsistent in demonstrating that this difference between bipolar depressed and unipolar depressed patients on tasks of executive function exists (Sweeney et al., 2000; Wolfe et al., 1987; Abra[illegible] et al., 1980).

Dysfunctions in mood disorder patients in the domain of executive function reflect higher order difficulties in problem solving, planning sequential actions, and working based on feedback to modulate or inhibit responses (Elliott, 2003). It is generally accepted that these functions are controlled by regions of the prefrontal cortex and frontal lobe, and there is substantial data which suggest that mood disorder patients display dysregulations of activity within this region, both at baseline and during task execution. In unipolar depressed patients at rest, previous studies have demonstrated dysregulations in brain activation in the dorsolateral, ventrolateral and orbitofrontal regions of the frontal lobe, often accompanied by changes in activity of the anterior cingulate (Drevets, 2000; Rubin et al., 1995; Mayberg et al., 1994; Biver et al., 1994; Bench et al., 1993; Dolan et al., 1992; Baxter 1989). Most consistently, a DLPFC hypoactivity is supported (Mayberg 2003). There are few imaging studies, however, which have examined bipolar depressed patients independently from unipolar depressed patients (Stoll et al., 2000). These limited published findings show a decrease in cerebral blood flow in the inferior frontal cortex (Rubin et al., 1995), and an increase in cerebral metabolism in the basal ganglia and thalamus (Baxter et al., 1989) in depressed bipolar patients compared to HCs.

There is no conclusive evidence for specific functional brain activity changes in depressed patients engaging in executive function tasks. Studies of major depressed patients completing the WCST, TOL test, verbal fluency task or Stroop test have not always demonstrated significant differences in activation relative to HCs (Rogers et al., 2004). What has been observed includes both increases and decreases in brain activation of the prefrontal cortex and anterior cingulate (Wagner et al., 2006; Goethals and al., 2005; Okada et al., 2003; Audenaert et al., 2002; Elliott et al., 1997). In bipolar patients, studies of executive function have demonstrated decreased activity of the right ventral and medial frontal cortex (Roth et al., 2006) and of the dorsolateral and VLPFC (Kronhaus et al., 2006, Blumberg et al., 2003) independent of state. Other studies, however, have found increased activity of the DLPFC and decreased activity of the anterior cingulate in euthymic bipolar patients completing the Stroop test (Gruber et al., 2004) as well as increased activity in the medial frontal, left inferior frontal and medial parietal cortex in patients during verbal fluency testing (Curtis et al., 2001). In depressed bipolar patients specifically, Blumberg et al. (2003) noted increased activity in the left ventrolateral prefrontal cortex, compared to a group of euthymic patients during the administration of a Stroop paradigm.

The current study aims to assess the presence of executive function deficits in the prefrontal cortex in patients suffering from bipolar depression (BPD) and MDD. Using fMRI, our goal is to delineate the differences between the patient groups on measures of brain activity in the prefrontal cortex during a battery of executive function tasks.

In particular, in this study, we have limited our evaluation to a comparison of unipolar major depressed patients and patients suffering from BP II. BP II, often underecognized (Berk et al., 2005), is characterized by periods of depression and hypomania. However, patients with BP II often present in a depressed state and do not report past hypomanic episodes (Berk et al., 2005). There has been a limited amount of neurobiological comparisons between BP I and BP II, and this is also true of the functional neuroimaging studies which have been carried out to date in BP (McGrath et al., 2004). In addition, some researchers have suggested that BP II could be considered to exist along a spectrum of mood disorders, flanked by BP I and MDD (Benazzi, 2007). While there are some clinical clues which may distinguish between a unipolar depression and BP II,such as age of onset (earlier in BP II) and the presence of atypical features (increased in BP II) (Berk et al., 2005), there is a lack of investigations aimed towards identifying a neurobiological distinction between these two disorders. This study attempts to distinguish between unipolar disorder and BP II by functional neuroimaging of executive dysfunction.

9.2 Methods

This study was approved by the Health Ethics Board at the University of Alberta, Faculty of Medicine and Dentistry and all subjects gave full informed consent.

9.2.1 Subjects

Sixteen patients suffering from MDD and eight patients suffering from BP II in a depressed state were recruited from a mood disorders rapid referral program run by Dr Peter Silverstone between February 2006 and March 2007. A full personal and family history was obtained and diagnosis was made using Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) criteria for BP and MDD (American Psychiatric Association, 1994), using the structured clinical interview for DSM-IV (SCID). Symptom severity for depression was determined using the 17-item HAM-D (Hamilton, 1960), and the MADRS (Montgomery and Asberg, 1979). Absence of manic symptoms was confirmed by the YMRS (Young et al., 1978). Past and present drug use was assessed and subjects were excluded based on current abuse of these substances.

9.2.2 Study Design

Patients underwent one fMRI scan, and brain activation was measured as they performed three different tasks, which are described in detail elsewhere (Bell et al., 2007, Chapter 7).

Tasks:

The three tasks; WCST, TOL task and a verbal fluency task based on a modification of the COWAT-FAS were administered in a blocked design. The paradigms are depicted in Figures 9.1, 9.2 and 9.3. Each was presented to the subjects visually by projection (Epson ELP-7000) onto a screen viewed while in the magnet. E-prime software was used to create and present paradigms, as well as to collect behavioural responses made by keypad (Cedrus RB-620). The WCST consisted of nine blocks (4 active tasks (110 sec each) and 5 control tasks (50 sec each)), the TOL task consisted of eight blocks (4 active tasks (60 sec each) and 4 control blocks (40 sec each)) and the verbal fluency task consisted of eleven blocks (5 active tasks (50 sec each) and 6 control task (50 sec each)).

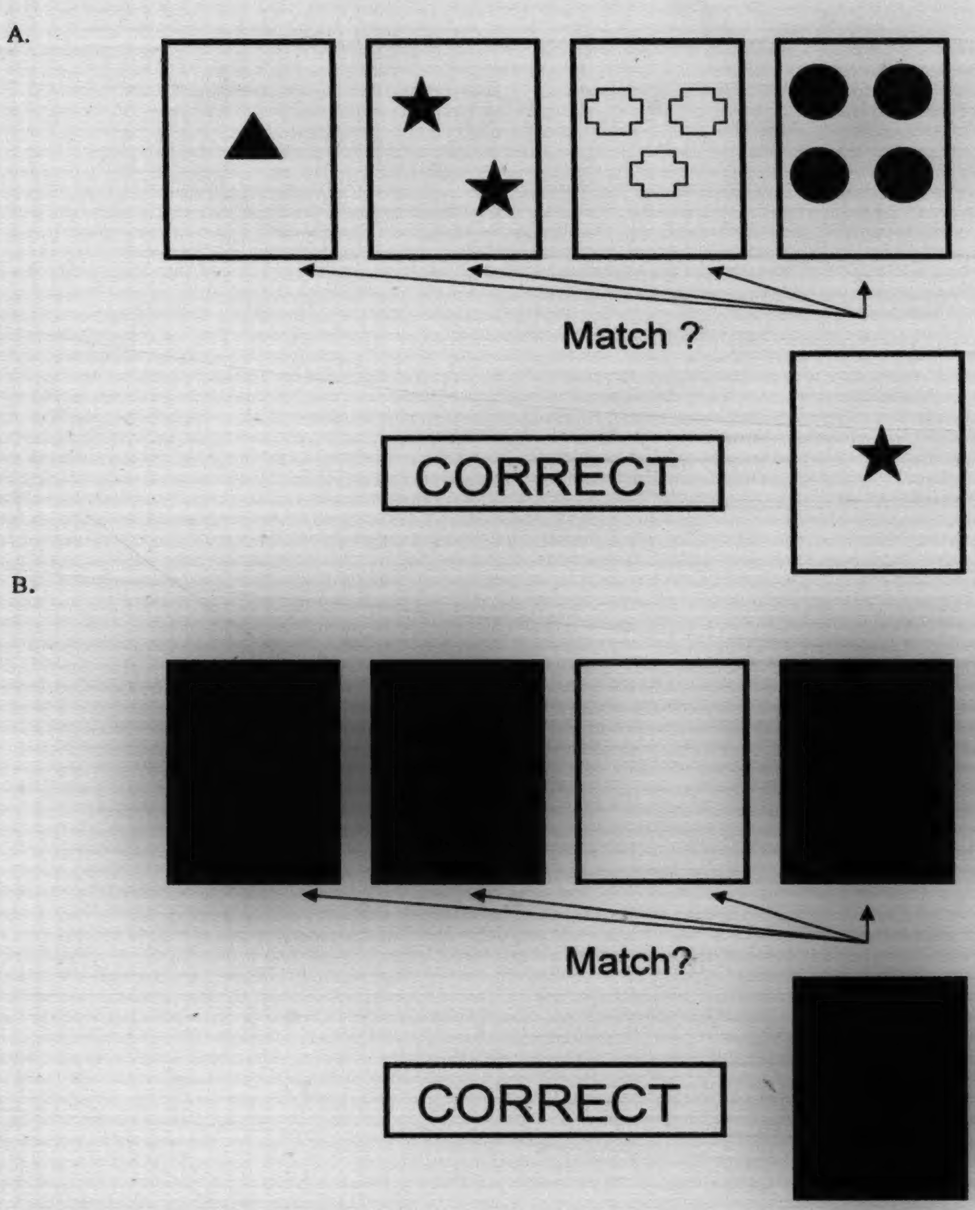


Figure 9.1A : The Wisconsin Card Sorting Task (WCST) active condition. B. Wisconsin Card Sorting Task (WCST) control condition. *Subjects must choose one of the static top four cards to match with the dealt bottom card. They modulate their response based on correct or incorrect feedback provided after each matching choice.*

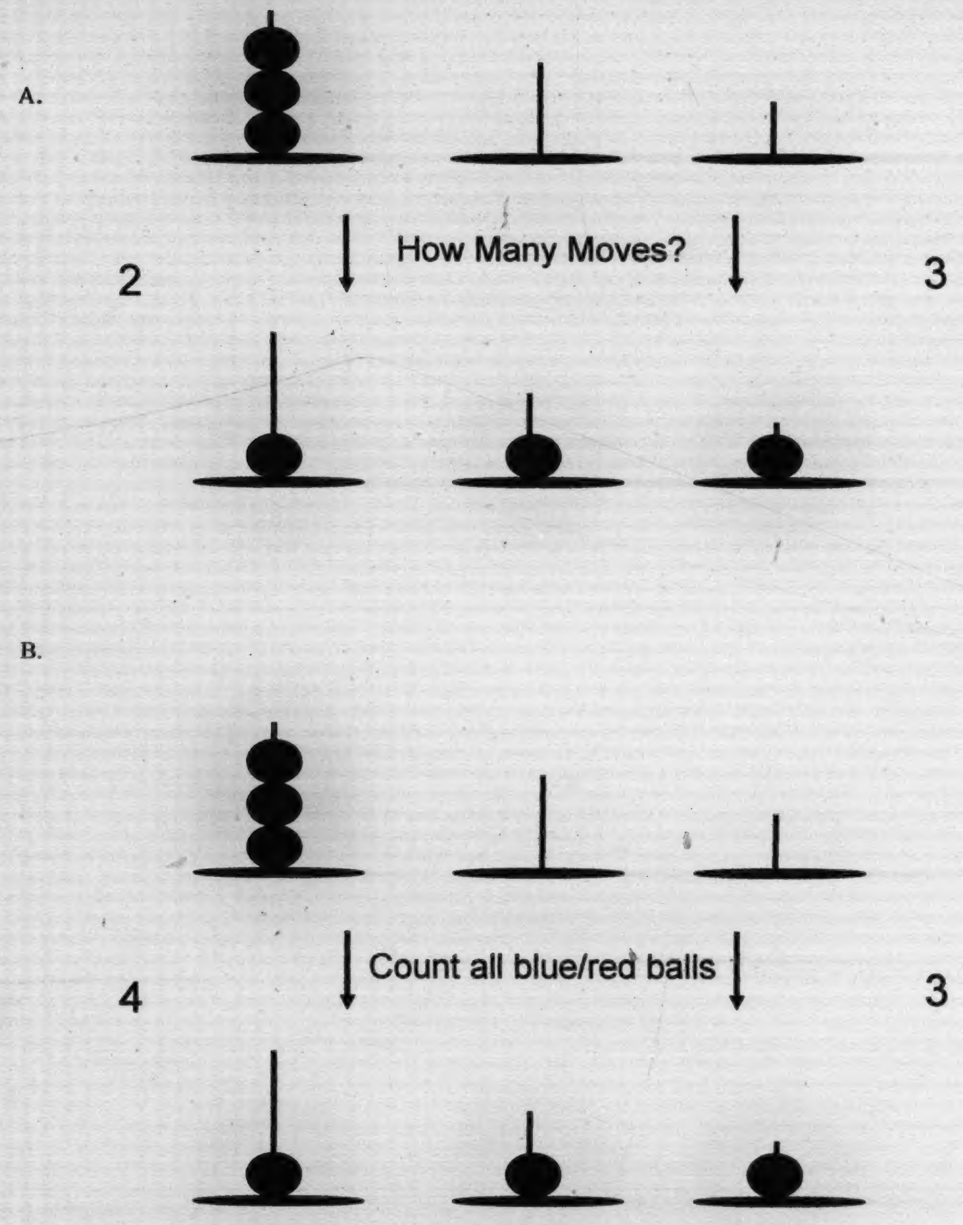
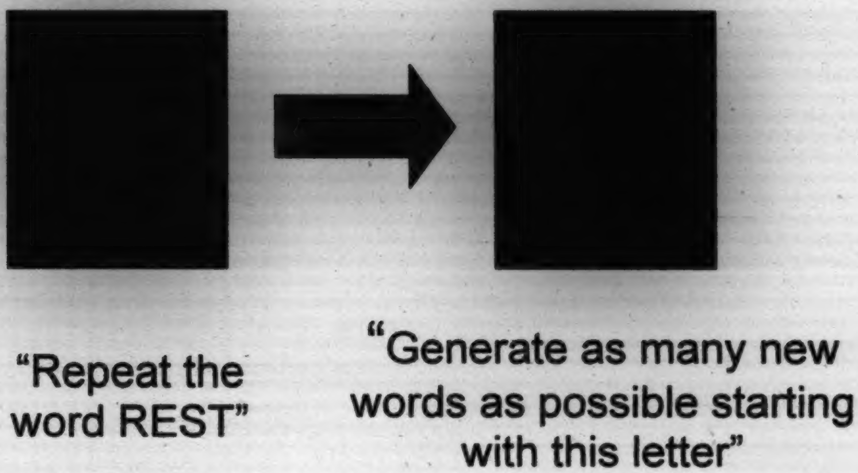

A.
2
How Many Moves?
3
B.
4
Count all blue/red balls
3

***Figure 9.2A : The Tower of London (TOL) active condition**. Subjects determine the minimum number of moves to get balls from top configuration to bottom and choose from 2 answers on either side of the screen. **B. The Tower of London (TOL) control condition**. Subjects count the number of red and blue balls on the screen and choose answer from 2 answers on either side of screen.*

Figure 9.3: Verbal fluency control and active tasks.

In the control condition subjects repeat the word "rest" until the word is removed from the screen and replaced by the active condition where subjects generate as many words as possible starting with the given letter.


"Repeat the word REST"
"Generate as many new words as possible starting with this letter"

9.2.3 Image Acquisition

The fMRI study was conducted on a 1.5-T Siemens Sonata scanner (Siemens, Erlangen, Germany) with a single shot eco-planar image (EPI) gradient echo sequence (TR = 2500ms, TE = 50msec, 3.4 x 3.4 x 4.0mm) to acquire 26 contiguous slices obtained at an oblique angle along the AC-PC line. A high resolution T1-weighted magnetization prepared rapid gradient echo sequence was also acquired during the imaging session to overlay the functional analysis.

9.2.4 fMRI Data Analysis

fMRI data analysis was conducted according to previously published methods (Willson et al., 2004, Bell et al., 2005). Pre-processing and analysis were performed using Statistical Parametric Mapping (SPM), 1999 version (SPM99 - Wellcome Department of Cognitive Neurology, University College London). All functional images were realigned during pre-processing to accommodate and correct for any head motion. Realignment was performed using a 6-parameter rigid body transformation and a mean image was created of the entire time series for each data set. The mean image was then spatially normalized to the MNI template brain using a 12-parameter affine transformation with 12 non-linear iterations and 7 x 8 x 7 basis functions. The spatial transformations derived from normalizing the mean image to the template were then applied to the T2* weighted realigned EPI functional images. Functional images were smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel to compensate for between subject variability and allow Gaussian random field theory to give corrected statistical inferences (Friston et al 1994). Initially a design matrix was created for each task and applied individually to each subject for analysis. A corrected threshold (p = 0.05) was applied to the analysis of the Verbal Fluency task, and an uncorrected threshold (p = 0.001) was applied to the more conservative activation maps observed in the WCST and the TOL task. Additionally, within each design matrix the data were high pass filtered to remove low-frequency drifts in the signal and low pass filtered using the hemodynamic response function to remove high frequency noise. The data were proportionally scaled to a global mean of 100.

For each subject the individual activation maps generated during single-subject analysis were used to identify the number of activated pixels and BOLD signal magnitude within each ROI. Image ROIs were constructed using AAL software (Tzourio-Mazoyer et al., 2002), running with MRIcro (Rorden and Brett, 2000). ROI boundaries were determined from previous literature resulting in five areas of interest; the right and left dorsolateral prefrontal cortex (RDLPFC, LDLPFC) (BA 9 and 46), the right and left ventrolateral prefrontal cortex (RVLPFC, LVLPFC) (BA 44,45 and 47), and the medial prefrontal cortex (mPFC) (BA 24, 25 and 32) (Goethals et al., 2004). Each ROI was then smoothed in SPM99 with an equivalent kernel (8mm) as the functional EPI images.

Within each ROI, in each task, the number of activated pixels was determined using a SVC. The BOLD signal magnitude in each ROI was determined using the MARSBAR toolbox for SPM (Brett et al 2002). The magnitude of the signal was calculated across a seven-voxel sphere centered on the *most* significantly active voxel in each ROI. The fitted response (or BOLD signal intensity change) is expressed in percentage of whole brain mean. Because the global brain mean in the voxel-wise analysis was scaled to 100, this signal change represents the percentage of signal change with respect to the global mean intensity of the scaled images. Subsequently statistical calculations for BOLD signal magnitude were based on the average response calculated from the plateau portion of the hemodynamic response (eight seconds after stimulus origination until stimulus termination) (Willson et al., 2004).

Comparisons of the number of activated pixels and BOLD signal were carried out using independent samples t-test between MDD patients and BPD patients. This comparison was made for the mPFC directly. Comparisons between the four regions of interest in the lateral prefrontal cortex (lPFC) were made by calculating the relative ratio of activity in one ROI vs the other areas. Student's t-tests were then used to compare these ratios between MDD patients and BPD patients and significance was set at $p \leq 0.05$.

9.3 Results

9.3.1 Subjects

Sixteen MDD patients (10 females, 6 males) and 8 BPD patients (BP II) (4 females, 4 males) underwent a functional imaging scan. The patient groups were on average the same age (p = 0.32; age ± SD; BPD, 33.1 ± 10.1; MDD, 37.6 ± 10.1). MDD patients had a Hamilton depression rating score of (± S.D.) 19.7 ± 4.4, compared to BPD patients with average ratings of 18.4 ± 1.6. On the MADRS scale, MDD patients scored an average of (± S.D.) 26.1 ± 1.3 and BPD patients scored 24.6 ± 2.4. These measures of severity of depression were not statistically different between patient groups. Manic symptoms, assessed by the YMRS were also not significantly different in our groups. MDD patients scored (± S.D.) 1.9 ± 2.0 and BPD patients scored 2.4 ± 1.0. Data from one MDD patient appeared corrupt on analysis of the WCST and two MDD patients were unable to complete the TOL task. Of the BPD patients, two were also unable to complete the expectations of the TOL task and their data was excluded. Patients were on a variety of medications. Of the MDD patients, fifteen were taking antidepressants, and five were receiving concomitant treatment with antipsychotics. Of the BPD patients four were taking lithium, four were on antipsychotics, five were on antidepressants and three were on anticonvulsants.

9.3.2 Functional Imaging Results

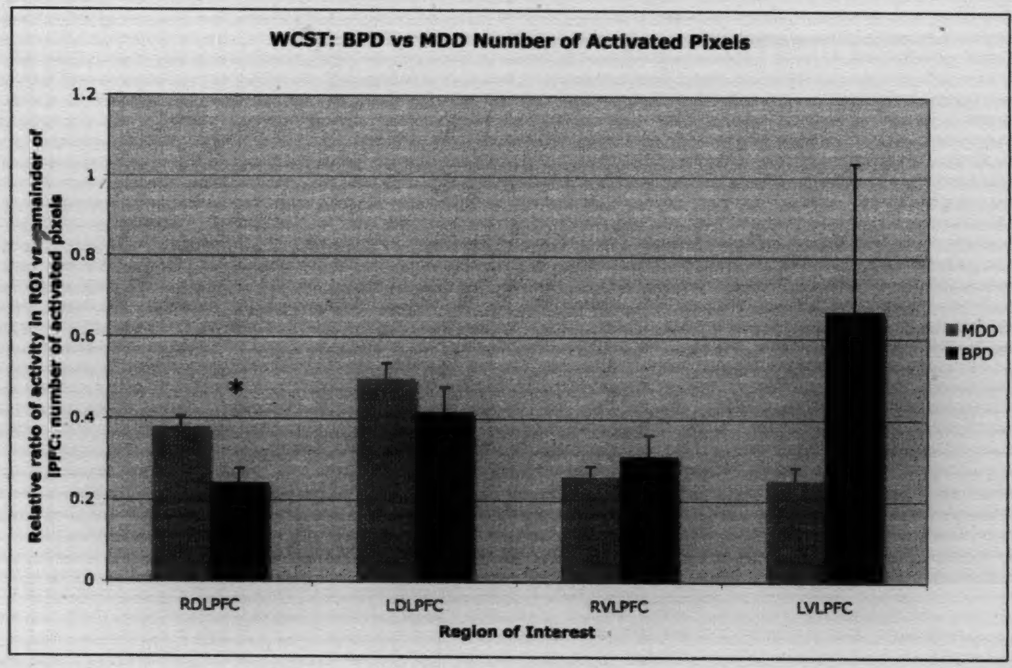
Wisconsin Card Sorting Task (WCST):

There were no significant differences between MDD patients and BPD patients on measures of either the number of activated pixels or the BOLD signal magnitude in the mPFC. Comparisons of the left and right DLPFC and VLPFC revealed a significant decrease in the number of activated pixels (p = 0.005) relatively in the right DLPFC in BPD patients (0.24 ± 0.03), compared to MDD patients (0.38 ± 0.03). As shown in Figure 9.4. There were no significant differences in the BOLD signal between BPD patients and MDD patients.

Figure 9.4: The relative ratio of activity (number of activated pixels) in the ROI vs. remainder of the lPFC in BPD patients and MDD patients in the WCST.

** equals p-value significant ≤ 0.05 level between group comparison of BPD patients and MDD patients.*

(Right DLPFC = RDLPFC; left DLPFC = LDLPFC; right VLPFC = RVLPFC; left VLPFC= LVLPFC)



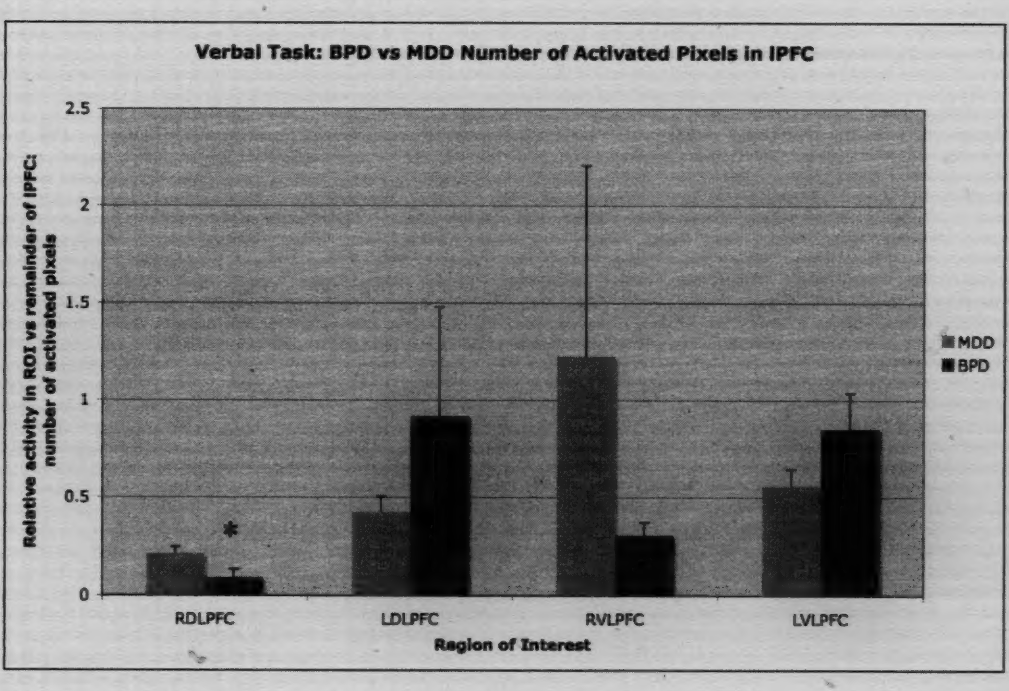
Verbal Fluency Task:

There were no significant differences between MDD patients and BPD patients on measures of the number of activated pixels or the BOLD signal magnitude in the mPFC. Comparisons between the right and left lPFC revealed significant differences between MDD patients and BPD patients in the right DLPFC (RDLPFC). MDD patients demonstrated significantly greater relative activation of the RDLPFC ($p = 0.04$) measured by the number of activated pixels (0.21 ± 0.03) during this task, compared to BPD patients (0.09 ± 0.04). As shown in Figure 9.5. There were no significant differences between patient groups on measures of the BOLD signal strength.

Figure 9.5: The relative ratio of activity (number of activated pixels) in the ROI vs. remainder of the lPFC in BPD patients and MDD patients in the Verbal Fluency Task.

** equals p-value significant ≤ 0.05 level between group comparison of BPD patients and MDD patients.*

(Right DLPFC = RDLPFC; left DLPFC = LDLPFC; right VLPFC = RVLPFC; left VLPFC= LVLPFC)

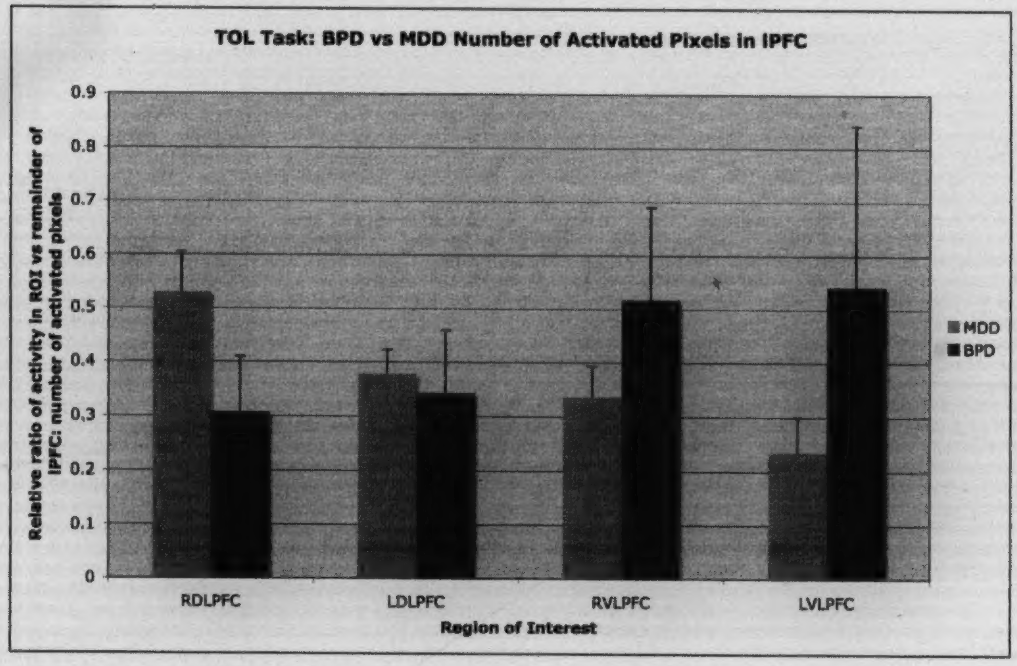


Tower of London (TOL) Task:

There were no significant differences between MDD patients and BPD patients on measures of the number of activated pixels or the BOLD signal magnitude in the mPFC or in measures of the lPFC activity. As shown in Figure 9.6.

Figure 9.6: The relative ratio of activity (number of activated pixels) in the ROI vs. remainder of the lPFC in BPD patients and MDD patients in the TOL task.

** equals p-value significant at the 0.05 level between group comparison of BPD patients and MDD patients. (Right DLPFC = RDLPFC; left DLPFC = LDLPFC; right VLPFC = RVLPFC; left VLPFC= LVLPFC)*



9.4 Discussion

The results from our study indicate that patients suffering from major depression significantly recruit the right DLPFC more than patients suffering from a depressive episode of BP II while carrying out tasks of executive function. Increased use of the right DLPFC in MDD patients is a consistent finding in two of the three tasks of executive function tested in our paradigm.

Executive function requires a coordination of cognitive procedures to achieve a goal. The cognitive problems to be solved require the subject to generate new strategies, modulate responses based on feedback and plan complex sequences of action (Elliott 2003). While patients with damage to the prefrontal cortex successfully complete more specific tasks of a cognitive battery, their cognitive dysfunction displays itself on tasks of executive function, and this is why the primary brain region thought to be responsible for the execution of these tasks is the prefrontal cortex (Elliott 2003). This also explains the focus in the current study on regions of interest in the prefrontal cortex.

Patients suffering from a variety of mood disorders, including BP and MDD, all demonstrate deficits on tests of executive function. Patients with BP in depressed, manic, hypomanic and euthymic states, demonstrate significantly worse performance on tasks of executive function (WCST, Stroop, Trail Making Test, and verbal fluency) than HCs (Malhi et al., 2007; Martinez-Aran et al., 2004), and other studies have suggested that patients in a depressed state are more vulnerable to verbal fluency deficits than non-symptomatic patients (Martinez-Aran et al., 2002). Previously, it had also been suggested that bipolar patients who are not acutely ill, and have no history of alcohol dependence do not suffer significant executive function deficits compared to healthy controls (van Gorp et al., 1998).

In major depression, assessments of cognitive function have demonstrated that acute patients suffer from deficits in executive functioning. Consistently, studies have demonstrated that depressed patients perform more poorly than healthy controls on the WCST and TOL task (Harvey et al., 2004; Fossati et al., 2001; Merriam et al., 1999; Austin et al., 2001, Purcell et al., 1997; Elliott et al., 1996; Axelrod et al., 1994; Franke et al.,1993). These deficits also potentially exist while patients are asymptomatic (Weiland-Fiedler et al., 2004).

Between patients groups a comparison of bipolar patients in the depressed phase (mostly BP I patients) and major depressed patients (Borkowska et al., 2001) has revealed that BPD patients are significantly more impaired than MDD patients in executive function, as measured by the WCST, the TMT, Stroop test and verbal fluency test. Results by Sweeney et al., 2000 contradict this finding and support that only a deficit in episodic memory, and not executive function, exists across bipolar and unipolar depressed patients. It is not clear, however, if BP I or BP II patients were combined in that study's sample. This possible effects of not making a distinction between the bipolar subtypes, though, was clarified by a more recent study comparing the cognitive deficits between BP I and BP II patients and healthy controls (Torrent et al., 2006). On tasks of executive function, the BP II subjects perform more poorly than healthy controls but not as poorly as BP I subjects on the Stroop task (Torrent et al., 2006). This highlights the need to examine BP I and BP II subjects independently in testing executive function.

The current study was designed to evaluate specifically the prefrontal cortex deficits, which we suggest, underlie the executive function deficits observed in MDD patients and BPD patients. In particular, this comparison involved BP II patients, a group with whom the distinction with major depression has not altogether been thoroughly investigated. In fact, BP II patients are often misdiagnosed as suffering from major depression, and while some features of BP II disorder (gender distribution, age of onset, mixed state and atypical features, length of illness) distinguish it from major depression (Berk et al., 2005), there have been no direct comparisons of neuropsychological executive function between these patient groups or examinations by functional imaging which have directly compared these groups (McGrath et al., 2004).

In functional imaging evaluations, BP I patients have demonstrated, relative to controls, decreased activation of right inferior frontal, medial frontal, left cingulate and left occipital gyrus (Roth et al., 2006); a decrease in activity in left ventral prefrontal cortex (Blumberg et al., 2003); a decrease in anterior cingulate activity along with an increase in DLPFC (Gruber et al., 2004), and a decrease in activity in the VLPFC and orbitofrontal cortex compared to HCs (Kronhaus et al., 2006), all on the Stroop task. In the most comprehensive examination of executive function in BP, Benabarre et al. (2005) examined the link between measures of brain activity and executive function in bipolar patients (I and II). In this study, researchers identified positive correlations between a patient's performance on neuropsychological testing and regional CBF, measured by SPECT scan. Increased errors on the WCST, or increased deficit on this task, researchers found, was correlated with a decrease in regional cerebral blood flow in the cerebellum and in the right posterior frontal lobe and an increase in regional cerebral blood flow in other areas, including the anterior frontal lobes and anterior cingulate (Benabarre et al., 2005). Although this study examined other tasks of executive function (Stroop test, verbal fluency test, TMT), WCST deficit was the only test found to correlate with cerebral blood perfusion in the frontal lobe.

In comparison, MDD patients tested on the Stroop task have shown an increase in activity of the anterior cingulate and LDLPFC (Wagner et al., 2006), and when tested on the TOL have shown a decreased activity in the cingulate cortex, in dorsolateral, medial and posterior regions of the prefrontal cortex and in temporal gyri (Elliott et al., 1997) as well as in right middle frontal cortex and left superior frontal gyrus (Goethals et al., 2005). We have previously shown that MDD patients recruit the left hemisphere lPFC less than healthy controls and increasingly utilize the right lPFC regions for executive function tasks (Bell et al., 2007, Chapter 7). This lateralization of function is consistent with Okada et al.'s (2003) finding of decreased left prefrontal cortex activation in depressed patients compared to healthy controls during the execution of a verbal fluency task. Our current results support a significantly greater activity in the right DLPFC in MDD patients compared to BPD patients.

Our study is the first to examine functional differences in executive tasks between unipolar depressed patients and a group of BP II depressed patients. Our previous results showed an increase in right hemisphere activity during executive function in MDD patients compared to HCs, and our current study demonstrates that MDD patients maintain an increased RDLPFC activity in executive tasks, compared to BP II patients. This is a noteworthy finding, because right DLPFC activity differentiates MDD patients from BP II depressed patients on two of three tasks of executive function in our study, therefore these tasks may act as a trait marker for major depression. There are limited data differentiating BP II patients from BP I patients and from MDD patients. Previously, it has been advocated that MDD and BP II disorder are along a continuum of overlapping mood disorders (Benazzi, 2007). However, our data would seem to suggest that brain activation during executive function may be a distinguishing feature between these two patient groups.

We must caution, however, that while our results support a significantly greater activity in the right DLPFC in MDD patients compared to BPD patients, our sample of bipolar patients was small and we may have failed to detect significant increases or decreases in other portions of the lPFC, where there was large variability in measures within our BP sample. In fact, as we observed in our comparison of MDD patients to healthy controls, we would have expected to see a relative decrease in other areas of the lPFC with the increase in right DLPFC. Possibly, with greater sample sizes a decrease in activity would have been significant in the LVLPFC, where we observed a reduction in activity in MDD patients across all three executive tasks, compared to BPD patients.

In conclusion, this is the first study to compare BP II patients in a depressed phase with a set of patients suffering from major depression on executive function, using neuroimaging. Our results suggest that MDD patients display a greater relative activation of the right DLPFC compared to BPD patients, during executive function. This finding of a trait difference between the two patient groups reinforces the idea that major depression and BP II disorder are functionally distinct disorders.

We hypothesized that depressed bipolar patients would demonstrate a significantly greater decrease in brain activation during executive function tasks, as they seem to perform more poorly than MDD patients on these tasks. We have observed a significant difference between these patients groups in the right dorsal prefrontal cortex. In this region, the increased activation during executive function in MDD patients compared to depressed BP patients seems to support a trait difference between patients suffering from these two disorders. These findings do not support the idea of a continuum between BP II and MDD disorders.

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Chapter 10. General Discussion and Conclusions

10.1 Overall Summary

Unipolar depression and bipolar disorder are prevalent and debilitating psychiatric disorders. Unfortunately, while there is an arsenal of medication used in the management of these mood disorders, many patients continue to suffer from subsyndromal depression, do not remit, or suffer from relapses. In addition to the symptoms characterizing the diagnosis of either MDD or BP, patients suffer a range of cognitive deficits including impairments in memory, attention, psychomotor speed and executive function. These deficits may impact the patient's ability to function at work and at home. Moreover, some cognitive impairment seems to persist beyond the symptomatic state, meaning that patients continue to have difficulties when their mood has resolved. This seems to be a particular concern in euthymic bipolar patients. Unfortunately, despite the development of new treatments and theraputic strategies, the pathophysiology of mood disorders is unclear. However, over the last several years we have begun to see the possible contribution of functional neuroimaging in delineating some of the neural pathways involved in major depression, resulting in the theoretical model of neurocircuitry proposed by Mayberg and colleagues.

The development of functional magnetic resonance imaging (fMRI) techniques in the 1990's opened the door to obtaining non-invasive high-resolution images of brain activity. Researchers then engaged in a number of investigations of mood induction and cognitive challenge in depressed patients and bipolar patients. Unfortunately, as studies vary widely in subject selection, paradigm selection, and data analysis methods, it has been difficult to compare and contrast investigations resulting in countless findings in patients of altered brain activation occurring in both directions. In addition, studies that test only one cognitive domain (most fMRI studies) may not present the most clear picture or valid representation of any brain activity changes occurring across the entire cognitive domain of interest. In neuropsychological testing, patients are tested on a variety of tasks within the cognitive domains to provide an assessement of impairment. Our studies have capitalized on the limitations of other studies, as we scan patients on numerous tasks to broaden the scope of our findings.

The experiments that were carried out in this thesis assessed regional brain activity changes in healthy controls, MDD patients and BPD patients. Using HCs, we engaged in the first functional imaging studies to assess changes in brain activity in a model of mania, as well as regional brain activity changes due to treatment with lithium and valproate, with the dextroamphetamine effect and without. The use of dextroamphetamine as a model for mania in HCs is particularly helpful in fMRI studies where patients are expected to engage in tasks for up to an hour. Our experience has shown that acutely manic patients, as expected, have difficulties maintaining their attention for this length of time, and may not follow instructions. However, we have found that healthy controls administered dextroamphetamine, while suffering similar (but milder) subjective and physiological effects, are able to complete the entire experiment. This has allowed us to observe the regional brain activity changes associated with mania, in HCs.

The effects of lithium and valproate on cell signaling at the neuronal level have continued to be the subject of intense investigation. However, our study was the first fMRI study to assess the medication effect of two prominent mood stabilizers, both on a model of mania and administered alone in healthy subjects. Medication effects are increasingly important because we see that patients, particularly bipolar patients, are on numerous medications during study participation. We must be aware of the ways in which psychiatric pharmacotherapy can impact functional imaging measures. These studies allowed us to draw conclusions about regional brain changes associated with the treatment of a model of mania and to infer the effects of mood stabilizers on regional brain activity in HCs.

In addition, we completed the only fMRI study which has compared BP II depressed patients to MDD patients on tasks of executive function. The delineation between the pathophysiology of BP II disorder, where patients suffer from hypomanic episodes, and MDD is unclear. BP II patients are often misdiagnosed as suffering from major depression and spend the majority of their time in the depressed state. There is some suggestion of a continuum between BP II depression and MDD, although BP II patients are still often lumped with BP I patients in research investigations. This factor, as well as a lack of comparisons between BP I and BP II patients, make the distinctions between these groups of particular interest.

In conclusion, the findings of this doctoral thesis are as follows: [1] Dextroamphetamine as a model of mania in healthy controls causes a decrease in brain activation across cognitive domains of working memory, attention and verbal fluency in a region-dependent manner. [2] Pre-treatment with the mood stabilizer lithium attenuates the decrease observed with dextroamphetamine administration in healthy controls in an attention task and a verbal fluency task. [3] Pre-treatment with the mood stabilizer valproate attenuates the decrease observed with dextroamphetamine administration in healthy controls in a working memory task. These effects occur in a region- specific manner. [4] Valproate attenuates the subjective effects of dextroamphetamine administration in healthy controls on measures of happiness, energy, alertness and lightheadedness, while lithium only attenuates the increase in happiness measured with dextroamphetamine administration in healthy controls. [5] Compared to placebo, healthy controls treated with lithium express a decrease in brain activation during a working memory task, and when treated with valproate express a decrease in brain activity in a verbal fluency task and attention task. [6] Males and female healthy controls express different brain activity across a variety of cognitive tasks, and these effects are inconsistent with behavioural performance on cognitive tasks. [7] MDD patients, compared to healthy controls, show a relative increased right hemisphere prefrontal activation during the completion of executive function tasks. [8] MDD patients, compared on executive task performance, have an increased activity of the right dorsolateral prefrontal cortex, compared to BP II depressed patients.

10.2 Limitations

In evaluating the studies contained in the current work, one must be aware of limitations that may influence the interpretation and generalization of the results.

Patient populations

When we engage in clinical research we must always be aware of difficulties that arise in the design and implementation of studies engaging patient samples. In our current patient work, we can identify several limitations, including; a) difficulty obtaining an accurate diagnosis, b) difficulty recruiting patients, c) patient performance in the magnet, d) medications effects in patient groups, and e) education level in patients.

As we have designed our last experiements to investigate the differences between MDD patients and BP II depressed patients, the diagnosis of these patients is paramount in the findings. In fact, because information in obtaining a psychiatric diagnosis is obtained by personal interview, it is difficult to distinguish between MDD and BP. It becomes even more difficult to distinguish between BP II and MDD patients, as BP II patients are often seen during a depressed state and do not report past hypomanic episodes. It is, therefore, very important that we obtain as much history of past mood episodes in these patients to make a correct diagnosis. We hope that maintaining consistency in the clinicians who interviewed and diagnosed patients in the study will have somewhat minimized the presence of misdiagnosed patients.

Another limitation of studying patient samples is the difficulty in recruiting patients. Unformtunately, this problem collides with the limitation of decreased power in functional imaging. In our studies of executive function, we have engaged patients and controls in very discrete tests of neural function. The result is that the fMRI signal obtained is on average less than 2% change in the active condition. In addition, there is substantial variability between subjects in the fMRI signal obtained during these tasks. This means that we need substantial power to detect significant differences between groups. Unfortunately, we found patient recruitment to be very difficult in our studies. Patients referred to Dr. Silverstone's mood rapid referral program were often mood disordered patients complicated by anxiety issues. Our intent, in this clinic, was to detect BP patients who may have been misdiagnosed as suffering from MDD. Unfortunately, this did not account for substantial amount of the patients seen. In addition, many patients were unable to participate in the study because of contraindications to MRI scan. We must acknowledge that limitations in recruitment, and therefore in patient sample size, and likely in low power, have impacted our ability to make far reaching conclusions from our patient work.

Additionally, the effects of performance or preferred matching of performance between controls and patient samples remains a topic of great discussion in fMRI. That is, what detriment to the fMRI signal is a patient group who cannot perform the fMRI tasks at the same level of controls? Or, should patients and controls perform different difficulties of tasks in order to assure similar performance levels? The answers to these questions are still not clear. Our own studies in healthy males and females have highlighted that performance on tasks has unpredictable effects on fMRI measures. In our studies of MDD and BP II patients, we found that performance (particularly reaction times) were significantly poorer in patient samples compared to HCs. Unfortinately, psychomotor slowing is one of a constellation of symptoms patients experience in a depressed episode, and this may impact their ability to perform the tasks to the same level as HCs. In addition, it may be that patients do not simply fail to perform as well as controls but may be unmotivated to perform the tasks. Again, motivational deficits are commonly present in patients suffering a depressed episode. The relationship between performance and fMRI signal will have to be further illucidated in order to solve the dilemma of patient performance in the magnet.

Our patient studies assess patients with active illness. Our studies in healthy controls have clearly suggested that lithium and valproate (commonly prescribed mood stabilizers) are independently able to alter brain function. Dealing with patient populations, we are often unable to obtain subject samples that are unmedicated. Indeed, in our patient samples, most patients were medicated; MDD patients were on antidepressants and BP patients were on a variety of mood stabilizers, atypical antipsychotics and antidepressants. In particular, teasing out the effects of medications in BP disorder is difficult because patients are on a variety of medications or combination of medications which have different mechanisms of action. We acknowledge that after previously demonstrating the significant effects of lithium and valproate on brain activation in HCS, that are patient studies have likely been counfounded by medication effects in both MDD and BP patient groups. Unfortunately, because we were interested in patients who were acutely depressed, we are limited ethically to prioritizing their treatment needs.

Finally, our results in MDD patients compared to HCs are somewhat compromised by baseline demographic differences between the groups. First, our patient group was significantly older than our HC group. Recruiting HCs from the university population is common practice, but may not represent the best comparison group, as the average age of the groups tends to be lower than patients. Although, our patient sample was actually highly varied around its mean age. More important, may be the fact that a university recruited HC population is more highly educated and may fall into a higher sociodemographic than psychiatric patient groups. In the future, it may be of benefit to match for IQ and/or educational level in patients and HCs.

Gender

Our investigations in HCs also highlighted the effects of gender on regional brain activity and performance in cognitive tasks and fMRI. Our findings show that there are substantial performance and brain activation differences between male and female HCs. In fact, many previous studies have found gender differences in brain activity (see Chapter 7 for a full review). There are additional male-female differences which may impact functional imaging results. In fact, females have been shown to have an increased global baseline CBF (Gur and Gur, 1990), and structural differences may also exist including differing proportions of grey and white matter between genders (Gur, 1999). Moreover, hormone changes in estrogen and progesterone levels have been demonstrated to cause changes in baseline CBF and CBF during performance of the WCST (Okhura et al., 1995; Berman et al., 1997). Other researchers have shown that high estrogen levels or estrogen therapy can affect regional brain activity in healthy women (Dietrich et al., 2001; Shaywitz et al., 1999). Unfortunately, because we did not assess the menstrual cycle phase of healthy women in our study we are unable to make any distinctions based on hormone levels or hormonal effects. The differences that we and others have observed between genders emphasizes the advantage or studying only one gender, likely males would be preferred due to decreased hormonal fluctuations. Unfortunately, in our patient studies, we feel that HCs of both genders had to be studied for comparison to patients because of the high proportion of female patients we recruited, and the increased prevalence of MDD in females. In the future, healthy control studies may benefit from a more focused approach in one gender sample.

Functional Imaging

We are faced with several difficulties in interpreting fMRI experiments. Current limitations in the interpretation of fMRI include; a) the meaning of the BOLD signal, b) linearity of the BOLD response c) the meaning of structure and function.

In fMRI the measurement of the BOLD signal only correlates with brain activation. Interpretting this signal as neural activation would be false. The hemodynamic response (BOLD signal) relies on many factors including blood flow, hemoglobin and cerebral metabolic rate of oxygen or glucose. Individual differences in age, fitness, health, heart efficiency, and blood vessel health could all affect the physiological processes contained in the BOLD response (Illes et al., 2006). This is to say nothing of the effects of psychiatric pathophysiology on these processes.

In addition, for statistical analysis we make the assumption that the BOLD signal is linear. That is to say that, each stimulus produces and equal hemodynamic response in the same brain region activated by the same. Making this assumption means that the presentation of many stimuli in succession produces a summed BOLD signal, which resembles a plateau of response. However, in making this assumption we rule out the idea that an area activated by a single stimulus may emit a different (i.e. reduced or increased) hemodynamic response to a secondary stimulus. In fact, it is possible that different brain regions exibit different properties when it comes to linearlity of the hemodynamic response. Unfortunately, by assuming that linearity occurs may lead to misinterpretations of the fMRI signal.

Last, in fMRI it is important that we do not jump to equate brain areas as subserving a specific function. Individuals who perform the same task equally may show different regions of brain activation, but they may also be using different strategies to solve the task resulting in the recruitment of differing regions. In addition, one should be careful not to jump to conclusions that areas of increased BOLD signal are areas specifically involved in the task, or subserving that role soley or distinctly. "… fMRI results do not definitively demonstrate that a brain region is involved in the task, but rather than the region is activated during the task" (Illes et al., 2007).

10.3 Future Directions

An extension of future work from this thesis, I hope, will be an application of the same methods to euthymic BP and MDD patients. I believe our findings in executive function in the depressed patients demonstrates that differences in brain function may exist between the two mood disorders. However, by introducing two additional patient groups, a euthymic BP group and a MDD euthymic group, we would have additional comparisons to make. Do functional differences resolve when patients are asymptomatic in one or both disorders? Because neuropsychological deficits still exist in euthymic patients, do the same functional changes exist? Are there additional trait related differences between MDD and BP II?

Functional imaging in psychiatry is aiding us to establish new neurocircuitry targets for the treatment of mood disorders and anxiety disorders, for example in deep brain stimulation therapy. In the future, the development of these and future therapeutics will only benefit from a greater understanding of the significance of the fMRI BOLD signal and its relationship with cellular function. This is a key area of development, as it will provide a greater context to the regional brain activity changes that are observed in functional imaging, and may result in a greater understanding of the pathophysiologies of these illnesses.

Regardless, it is my belief that one should and make clear and concise goals in carrying forward fMRI research. It is still largely unclear how fMRI findings can impact treatment, diagnosis or exert great benefit in the practice of clinical psychiatry. Due to its complicated nature, and the varied interpretations that may present, one should always put forward strong hypothesis driven reseatch in the field. I believe that fMRIs strongest contribution in psychiatry will be in answering specific questions about brain function and neural circuitry in psychiatric disease, rather than in detecting the origin of psychiatric illness.

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